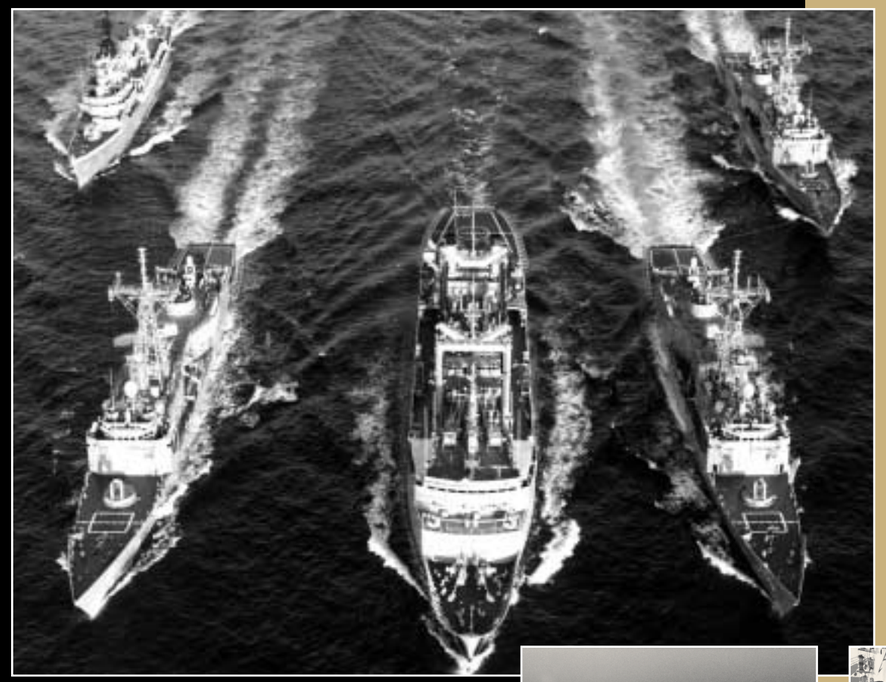
Australian Gulf War Veterans' HEALTH STUDY 2003

volume

1



MONASH UNIVERSITY

HSA Health Services Australia

The Hon Danna Vale MP
Minister for Veterans' Affairs
Parliament House
CANBERRA ACT 2600

Dear Minister

I have pleasure in submitting the final report of the *Australian Gulf War Veterans' Health Study* conducted by a team from Monash University, headed by Associate Professor Malcolm Sim, assisted by his research team and Health Services Australia. This study has investigated the health of 1456 Australian male and female Gulf War veterans.

I would like to take this opportunity to thank the members of the Australian Gulf War Veterans Health Study Consultative Forum for their assistance and cooperation during the conduct of the study:

- Colonel Peter Warfe – representing the Department of Defence;
- Dr Kerry Delaney – representing the Returned and Services League;
- Mr Peter Alexander CMG OBE OAM – representing the Australian Veterans and Defence Services Council;
- Commodore Mike Flynn – representing the Naval Association;
- Commodore Michael Dowsett – representing the Regular Defence Welfare Association;
- Mr Neil MacDonald – representing the Aboriginal and Torres Strait Islander Veterans' Association;
- Mr David Watts – representing the Gulf War Veterans' Association;
- Mr Colin Doust – representing the Totally and Permanently Incapacitated Federation;
- Mr Bill Hindson MC MG – who replaced Mr Doust (above);
- Ms Judy Swann – representing the National Consultative Group of Service Families;
- Major Gary Skewes – representing the Defence Safety Management Agency;
- Mr Paul Evans – Office of the Minister for Veterans' Affairs; and
- Mr David Cooke - representing the Department of Defence.

The Report's preparation was supervised by the Scientific Advisory Committee (SAC), chaired by Professor Terry Dwyer, AM, ably assisted by Professor Tania Sorrell, Dr Kerry Delaney, Professor Sandy MacFarlane and Dr Leigh Blizzard.

The Department of Veterans' Affairs undertook most of the work in contacting and recruiting participants to the study and my appreciation goes to the team led by Mr Bob Connolly. I would also like to thank Dr Keith Horsley, the Director of Research Studies and the other departmental staff who worked on the study.

Yours sincerely

Neil Johnston
PRESIDENT
4/2/03

Menzies Centre for

Population Health Research

ABN 30 764 374 782

University of Tasmania
The Menzies Building
Private Bag 23
Hobart Tasmania 7001
Australia

Phone: (03) 6226 7700
Facsimile: Nat: (03) 6226 7704
Int: +61 3 6226 7704
http://www.menzies.utas.edu.au

23 December, 2002

Mr Ian Campbell
Acting President
Repatriation Commission
PO Box 21
Woden ACT 2606

Dear Mr Campbell,

I have pleasure in approving presentation of study findings of the Australian Gulf War Veterans' Health Study. The Scientific Advisory Committee, under my chairmanship, approved protocol and monitored progress from a scientific point of view.

Yours sincerely,

Professor Terry Dwyer AM
Director

MONASH
UNIVERSITY

Department of Epidemiology
& Preventive Medicine
Central & Eastern Clinical School
Faculty of Medicine,
Nursing & Health Sciences

Associate Professor Malcolm Sim
Head of Unit
Unit of Occupational & Environmental Health
Telephone +61 3 9903 0582
Facsimile +61 3 9903 0556
malcolm.sim@med.monash.edu.au
http://www.med.monash.edu.au/epidemiology

Friday, 20 December 2002

Professor Terry Dwyer
Chair, Scientific Advisory Committee
Australian Gulf War Veterans' Health Study
Menzies centre for Population Health Research
University of Tasmania
GPO Box 252-23
Hobart TAS 7001

Dear Professor Dwyer,

RE: Australian Gulf War Veterans' Health Study

I have great pleasure in submitting to you for final Scientific Advisory Committee approval the research report containing the findings of the Australian Gulf War Veterans' Health Study. As Principal Investigator, I am submitting this report on behalf of the rest of the Monash research team and also on behalf of our collaborator, Health Services Australia.

I would also like to take this opportunity to thank you and the other members of the Scientific Advisory Committee for your helpful suggestions and advice during the course of this study.

Yours sincerely,

Associate Professor Malcolm Sim
Principal Investigator
Australian Gulf War Veterans' Health Study

Mailing address:
DEPARTMENT OF EPIDEMIOLOGY
& PREVENTIVE MEDICINE
Central & Eastern Clinical School
Alfred Hospital
Prahran, Victoria 3181, Australia
Telephone: +61 3 9903 0555
Facsimile: +61 3 9903 0556
Deliveries: 3rd Floor, 553 St Kilda Road, Melbourne

ABN: 12 377 614 012

A Member of:
MONASH PUBLIC HEALTH
A Partner in the:
VICTORIA CONSORTIUM FOR PUBLIC HEALTH
COOPERATIVE RESEARCH CENTRE FOR WATER QUALITY AND TREATMENT

Authors

Monash University
Associate Professor Malcolm Sim, Principal Investigator

Associate Professor Michael Abramson

Associate Professor Andrew Forbes

Dr Deborah Glass

Ms Jill Ikin

Mr Peter Ittak

Dr Helen Kelsall

Dr Karin Leder

Mr Dean McKenzie

Professor John McNeil

Health Services Australia (HSA)
Health Services Australia Team, consisting of doctors, nurses and psychologists

Other Institutions
Associate Professor Mark Creamer, Australian Centre for Posttraumatic Mental Health, University of Melbourne

Dr Lin Fritschi, University of Western Australia (Mortality and Cancer Study only)

Table of contents

Volume 1

Authors 1
Table of contents 2
Executive summary 12
Introduction 12
Study aims 12
Methods 13
Recruitment, demographics and non-Gulf War exposures 13
Gulf War and other exposures 14
Summary of health findings 14
Strengths and limitations of the study 17
Recommendations 18
Acknowledgments 20
List of abbreviations 22
1. Introduction 28
2. Australian involvement in the Gulf War 29
2.1 The Gulf Region 29
2.2 Australian Deployment in the Gulf War 29
2.2.1 Damask I 30
2.2.2 Damask II 30
2.2.3 Damask III 31
2.2.4 Clearance Diving Team 3 31
2.2.5 Task Group Medical Support Elements on USNS Comfort 32
2.2.6 Operation Habitat 33
2.2.7 The United Nations Special Commission (UNSCOM) 33
2.2.8 Summary of ADF Deployments 33
2.2.8.1 Nominal Roll 34
3. Review of literature on exposures during the Gulf War 39
3.1 Introduction 39
3.2 Smoke from oil well fires (SMOIL) 40
3.2.1 Background 40
3.2.2 Plume dispersal 41
3.2.3 SMOIL exposure measurements 44
3.2.4 SMOIL exposure recall by veterans 46
3.3 Particulate matter 46
3.4 Psychological stressors 47
3.5 Immunisations and other prophylactic medications 48
3.6 Pyridostigmine bromide 50
3.7 Pesticide use 51
3.7.1 Insect repellent use 52
3.8 Biological and chemical weapons 53
3.9 Interactions between pesticides, PB and chemical warfare agents 56
3.10 Depleted uranium 56
3.11 Infectious disease agents 58
3.12 Other exposures 59
3.13 Multi-exposures and recall bias 60
3.14 Summary 60

4. Review of health studies 63
4.1 Scope of review of health studies literature 63
4.2 History of Gulf War veterans' health research 63
4.3 Symptoms 71
4.4 Factor analysis 73
4.5 Medical conditions 76
4.6 Demographics and lifestyle factors 77
4.7 Psychological health 78
4.8 Respiratory health 80
4.9 Infectious diseases 84
4.10 Immunisations 86
4.11 Chronic fatigue and immunological markers 87
4.12 Neurological symptoms 89
4.13 Musculoskeletal 92
4.14 Skin 93
4.15 Gastrointestinal conditions 94
4.16 DU related health problems 95
4.17 Reproductive outcomes 95
4.18 Cancer 96
4.19 Hospitalisations, medical care utilisation due to illness, functional impairment and limitation of work 97
4.20 Mortality 99
4.21 Self-referral evaluation programs 100
4.22 Summary 103
5. Cross-sectional study methods 107
5.1 Aims and objectives 107
5.2 Study design 107
5.3 Study population 108
5.3.1 Definition of the Gulf War veteran group 108
5.3.2 Definition of the comparison group 108
5.4 Sample size 109
5.4.1 Gulf War veteran group 109
5.4.2 Comparison group 109
5.5 Contact strategy and recruitment procedures 110
5.5.1 DVA-based Contact and Recruitment team 110
5.5.2 Contact procedures 110
5.5.3 Methods to maximise participation 111
5.5.4 Participation options 112
5.5.5 Telephone-questionnaire option 112
5.5.6 Administration of appointments for medical assessments 112
5.6 Data collection instrumentation and measures 113
5.6.1 Postal self-administered questionnaire 114
5.6.1.1 Demographic information 115
5.6.1.2 Exposure assessment 115
5.6.1.2.1 History of military service postings 116
5.6.1.2.2 Gulf War deployment history and specific exposures 117
5.6.1.2.3 Active (war or peacekeeping) deployment history and deployment exposures 118
5.6.1.2.4 Military Service Experience questionnaire 119
5.6.1.2.5 Civilian occupational history 120

5.6.1.3 Health outcomes assessment 120
5.6.1.3.1 Short-Form-12 Health Survey (SF-12) 120
5.6.1.3.2 Twelve item General Health Questionnaire (GHQ-12) 121
5.6.1.3.3 Symptom questionnaire 122
5.6.1.3.4 Neuropathic symptom questionnaire 122
5.6.1.3.5 Doctor diagnosed or treated medical conditions 122
5.6.1.3.6 General medical history 123
Hospitalisation 123
Functional impairment due to illness or injury 123
Current use of medication 123
Family history 123
5.6.1.3.7 Cigarette smoking and tobacco use 123
5.6.1.3.8 Alcohol consumption 123
5.6.1.3.9 Posttraumatic Stress Disorder Checklist – S (PCL-S) 124
5.6.1.3.10 Reproductive health outcomes 124
5.6.1.4 Nomination of a medical practitioner to receive a copy of their medical report 125
5.6.2 Medical assessment 125
5.6.2.1 Nurse-administered data collection 125
5.6.2.1.1 Informed Consent 126
5.6.2.1.2 Standardised measurement of height, weight, hip and waist circumference 126
Body mass index 127
Waist circumference and waist-to-hip ratio 127
5.6.2.1.3 Blood pressure 127
5.6.2.1.4 Visual acuity 128
5.6.2.1.5 Symptoms of tiredness or fatigue 128
5.6.2.1.6 Spirometry 129
5.6.2.1.7 Skin prick testing for common allergens 130
5.6.2.1.8 Respiratory Health Questionnaire 130
5.6.2.1.9 Laboratory investigations and pathology service 131
Laboratory investigations 131
Storage of samples for later analysis (overview) 131
Storage of samples for possible analysis within 12 months 132
Indefinite storage of a serum sample 133
Pathology service 133
5.6.2.1.10 Urinalysis 133
5.6.2.2 Psychologist's assessment 133
5.6.2.2.1 Psychological assessment procedure 134
5.6.2.2.2 Modifications to the posttraumatic stress disorder module 135
5.6.2.3 Medical examination 135
5.6.2.3.1 Physical examination 136
5.6.2.3.2 Assessment of symptoms of extreme tiredness or fatigue 137
Lymphocyte subsets 139
5.6.2.3.3 Review of the doctor diagnosed or treated medical conditions section of the postal questionnaire 139
5.6.2.3.4 General health questions and additional findings 140
5.6.2.3.5 Fitness test 140
5.6.2.3.6 Feedback to Participants 141
5.6.3 Telephone questionnaire participants 141

5.6.4 Consistency and validation measures and other sources of data 141
5.6.4.1 Access to ship's records 141
5.6.4.2 Comparison of self-reported information with Defence policies 141
5.6.4.3 Access to previous medical records 142
5.6.5 Blinding 142
5.6.6 Pilot study 142
5.6.7 Study Protocol 142
5.6.8 Study Procedures Manuals 143
5.6.9 Training 143
5.6.10 Communication 143
5.6.11 Data management 144
5.6.11.1 Transfer of medical data 144
5.6.11.2 Data checking, processing and coding and data entry 144
5.6.11.3 Methods to ensure privacy of medical data 145
5.6.11.4 Long-term storage of data 145
5.6.11.5 Data quality 146
5.6.11.6 Confounders and bias 146
5.6.11.7 Power considerations 146
5.6.11.8 Statistical analysis 147
5.6.11.9 Exploration of symptom clusters 149
5.6.12 Research Team 149
5.6.12.1 The Department of Epidemiology & Preventive Medicine, Monash University 150
5.6.12.2 Health Services Australia 150
5.6.13 Scientific Advisory Committee 150
5.6.14 Consultative Forum 151
5.6.15 Ethics Committees' Approvals 151
6. Recruitment 152
6.1 Recruitment categories 152
6.1.1 Ineligible subjects 152
6.1.2 Eligible subjects 152
6.1.2.1 Not recruitable categories 152
6.1.2.2 Recruitable categories 152
6.2 Recruitment results 153
6.2.1 Final eligible sample sizes 153
6.2.2 Recruitment outcomes for Gulf War veterans and the comparison group 153
6.2.2.1 Total eligible sample 153
6.2.2.2 Eligible sample by service type 154
6.3 Comparison of study participants and non-participants. 159
6.3.1 Participants compared with all non-participants. 159
6.3.2 Comparison of study participants with telephone questionnaire-only subjects 162
6.4 Investigation of possible participation bias 163
6.4.1 Method 1: Grouped data assessment of participation bias 165
6.4.2 Method 2: Individual data imputation-based assessment of participation bias. 167
6.5 Discussion 168
6.6 Technical Supplement – Details of the imputation procedure for non-participation 172
7. Demographic, socioeconomic and lifestyle factors 173

7.1 Aims 173
7.2 Research questions 173
7.3 Methods and materials 173
7.3.1 Subjects 173
7.3.2 Measurement of demographic and socioeconomic variables 173
7.3.3 Measurement of cigarette smoking and tobacco use 174
7.3.4 Measurement of alcohol consumption 175
7.4 Results 175
7.4.1 Demographic and socioeconomic variables 175
7.4.2 Cigarette smoking and tobacco use 177
7.4.3 Alcohol consumption 177
7.5 Discussion 179
7.5.1 Summary of findings 180
8. Reported Gulf War and other exposures 181
8.1 Aims 181
8.2 Research questions 181
8.3 Results 182
8.3.1 Service characteristics of the Gulf War deployment 182
8.3.2 Other active deployments 184
8.3.3 Immunisations and preventive medications reported for the Gulf War deployment 186
8.3.4 Self-reported psychological stressors during Gulf War service and during non-Gulf War service 188
8.3.4.1 Psychological stressors during Gulf War service 191
8.3.4.2 Psychological stressors during non-Gulf War service 193
8.3.5 Self reported chemical and environmental exposures during the Gulf War and other active deployments 193
8.3.5.1 Self-reported chemical and environmental exposures during the Gulf War 195
8.3.5.2 Self-reported chemical and environmental exposures on other active deployments 197
8.3.6 Development of chemical and environmental exposure metrics related to the Gulf War deployment 197
8.3.7 Other occupational exposures during the whole military career and during civilian careers 199
8.4 Discussion 199
8.4.1 Summary of findings 203
Volume 2
9. General health 205
9.1 Aim 205
9.2 Research questions 205
9.3 Definitions of general health outcomes 205
9.3.1 Self-reported symptom definitions 205
9.3.2 Self-reported medical conditions definitions 206
9.3.3 Hospitalisations, functional impairment and current use of medication 206
9.3.4 SF-12 Health Survey scoring 206
9.3.5 Physical health status definitions 207
9.3.5.1 Body mass index 207
9.3.5.2 Waist circumference and waist-to-hip ratio 207
9.3.5.3 Blood pressure 207

9.3.6 Gulf War exposure measures 208
9.4 Results 208
9.4.1 Symptoms 208
9.4.1.1 Comparison by service type 214
9.4.1.2 Total number of self-reported symptoms 216
9.4.2 Medical conditions 217
9.4.2.1 Self-reported medical conditions first diagnosed in 1991 or later 217
9.4.2.2 Comparison by service type 222
9.4.2.3 Total number of self-reported medical conditions 224
9.4.2.4 Doctor's assessment of the likelihood of self-reported medical conditions 224
9.4.2.5 Self-reported doctor medical conditions first diagnosed in 1990 or earlier 225
9.4.3 Hospitalisations, functional impairment due to illness or injury, and current use of medication 226
9.4.4 SF-12 Health Survey 226
9.4.5 Physical measures of general health 229
9.4.5.1 Height, weight, body mass index, waist and hip circumference and waist-to-hip ratio 229
9.4.5.2 Blood pressure 230
9.4.5.3 Fitness test 231
9.4.6 Gulf War veteran group subanalysis 232
9.5 Discussion 240
9.5.1 Summary of findings 246
10. Laboratory investigations 248
10.1 Aim 248
10.2 Research questions 248
10.3 Definitions 248
10.3.1.1 Overview of parameters for analysis 248
10.3.1.2 Laboratory reference intervals 249
10.3.1.3 Definitions of laboratory investigation outcomes 249
10.4 Results 250
10.4.1 Quality control 250
10.4.2 Gulf War vs non-Gulf War comparisons 251
10.4.2.1 Haematological test results 251
10.4.2.2 Biochemical test results 254
10.4.2.3 Liver function test results 256
10.4.2.4 Serological test results 259
10.4.2.5 Urinalysis results 260
10.4.3 Gulf War veteran group subanalysis 261
10.5 Discussion 261
10.5.1 Summary of findings 263
11. Psychological health 265
11.1 Aim 265
11.2 Research questions 265
11.3 Methods and materials 265
11.3.1 Measurement of psychological health 265
11.3.1.1 Composite International Diagnostic Interview, CIDI-Auto 2.1 265
11.3.1.2 12-item General Health Questionnaire (GHQ-12) 267
11.3.1.3 Posttraumatic Stress Disorder Checklist-S (PCL-S) 267

11.3.1.4 Alcohol Use Disorders Identification Test (AUDIT) 268
11.3.2 Gulf War exposure measures 268
11.4 Results 268
11.4.1 CIDI-defined DSM-IV disorders 268
11.4.2 12 item General Health Questionnaire (GHQ-12) 275
11.4.3 Posttraumatic Stress Disorder Checklist (PCL-S) 276
11.4.4 Alcohol Use Disorders Identification Test (AUDIT) 277
11.4.5 All Gulf War veterans versus comparison group subjects who had been on active deployments 278
11.4.6 Gulf War veteran group subanalysis: the effects of Gulf War-related exposures on psychological disorders in Gulf War veterans 279
11.4.7 Investigation of possible participation bias 286
11.5 Discussion 288
11.5.1 Summary of findings 294
12. Respiratory health 295
12.1 Aims 295
12.2 Research questions 295
12.3 Definitions of respiratory health outcomes 295
12.3.1 Respiratory symptom definitions 296
12.3.2 Respiratory condition definitions 296
12.3.3 Lung function definitions 296
12.3.4 Atopy definition 297
12.4 Gulf War exposure measures 298
12.5 Results 298
12.5.1 Respiratory symptoms 298
12.5.2 Respiratory conditions 299
12.5.2.1 Atopy 300
12.5.3 Lung Function Tests (spirometry) 300
12.5.4 Respiratory examination findings 302
12.5.5 Gulf War veteran group subanalysis 303
12.6 Discussion 306
12.6.1 Summary of findings 310
13. Neurological health 312
13.1 Aim 312
13.2 Research questions 312
13.3 Definition of neurological health outcomes 312
13.3.1 Neuropathic symptoms definition 312
13.3.2 Neuropathic disorder definition 312
13.3.2.1 A neuropathic disorder defined by neuropathic symptoms and neurological signs 313
13.3.2.2 A neuropathic disorder defined by a neuropathy impairment score 313
13.3.3 Myopathy definition 314
13.3.4 Disorders of peripheral motor neurones or their axons definition 314
13.3.5 Central nervous system disorder definition 314
13.3.6 Epilepsy definition 315
13.4 Results 315
13.4.1 Neuropathic symptoms and disorders 315
13.4.1.1 Neuropathic symptoms 315
13.4.1.2 Neuropathic disorders 318

13.4.2 Symptoms or signs indicative of myopathy, disorders of peripheral motor neurones or their axons, central nervous system disorder and epilepsy 320
13.4.3 Gulf War veteran group subanalysis 320
13.5 Discussion 325
13.5.1 Summary of findings 327
14. Chronic fatigue syndrome 329
14.1 Aim 329
14.2 Research questions 329
14.3 Definitions and classification of fatigue 329
14.3.1 Definitions of fatigue and chronic fatigue syndrome 329
14.4 Results 332
14.4.1 Fatigue and chronic fatigue syndrome 332
14.4.1.1 Fitness test results 333
14.4.2 Immunological profile of cases of chronic fatigue syndrome 333
14.4.3 Gulf War veteran group subanalysis 335
14.5 Discussion 335
14.5.1 Summary of findings 338
15. Health of female Gulf War veterans 340
15.1 Aim 340
15.2 Research questions 340
15.3 Results 340
15.3.1 Recruitment 340
15.3.2 Demographic, socioeconomic and lifestyle factors 341
15.3.3 Reported Gulf War and other exposures 342
15.3.3.1 Service characteristics of female Gulf War veterans during the Gulf War 343
15.3.3.2 Other active deployments 343
15.3.3.3 Immunisations and preventive medications reported for the Gulf War deployment 343
15.3.3.4 Self reported psychological stressors during Gulf War service and during non Gulf War service 344
15.3.3.5 Self reported chemical and environmental exposures during the Gulf War and other active deployments 346
15.3.3.6 Other occupational exposures during military postings and during civilian occupations 347
15.3.4 General health 348
15.3.4.1 Symptoms 348
15.3.4.2 Medical conditions 350
15.3.4.3 Hospitalisations, functional impairment and use of medications 352
15.3.4.4 Short-Form-12 Health Survey (SF-12) 352
15.3.4.5 Height, weight and Body Mass Index 352
15.3.4.6 Waist, hip, and waist-to-hip ratio 353
15.3.4.7 Blood Pressure 353
15.3.4.8 Fitness test 353
15.3.5 Laboratory investigations 353
15.3.6 Psychological health 355
15.3.6.1 CIDI-defined psychological disorders 355
15.3.6.2 GHQ-12, PCL-S and AUDIT 356
15.3.7 Respiratory health 356
15.3.7.1 Self reported respiratory symptoms and conditions 356

15.3.7.2 Spirometry 357
15.3.8 Neurological health 357
15.3.9 Chronic fatigue and immunological investigations 358
15.3.10 Reproductive outcomes 358
15.3.11 Cohort study of mortality and cancer 359
15.4 Discussion 359
15.4.1 Summary of findings 361
16. Reproductive health outcomes 362
16.1 Aim 362
16.2 Research questions 362
16.3 Methods and materials 362
16.4 Results 363
16.4.1 Fertility difficulties 363
16.4.2 Pregnancy outcomes 364
16.4.3 Health of live born children 364
16.4.4 Validation of reports of children with cancer 365
16.5 Discussion 365
16.5.1 Summary of findings 367
17. Cohort study of mortality and cancer 368
17.1 Aim 368
17.2 Research questions 368
17.3 Methods 368
17.3.1 Cohort composition 368
17.3.2 Registry matching process 369
17.3.2.1 Matching process 369
17.3.3 Data analysis and statistics 370
17.3.3.1 Cohort study periods 370
17.3.3.2 Calculation of person-years 370
17.3.3.3 Population cancer and death rates 371
17.3.3.4 Calculation of rate ratios, standardised cancer incidence ratio and standardised mortality ratios 371
17.4 Results 371
17.4.1 Cohort composition 371
17.4.1.1 Demographic characteristics 371
17.4.1.2 Person years of follow-up 372
17.4.2 Mortality results 372
17.4.3 Cancer results 373
17.5 Discussion 374
17.5.1 Summary of findings 377
18. Factor analysis of self-reported symptoms 378
18.1 Aim 378
18.2 Research questions 378
18.3 Methods 378
18.4 Results 380
18.4.1 Factor analysis of self reported symptoms among Gulf War veterans 380
18.4.2 Factor analysis of symptoms in the comparison group 383
18.5 Discussion 386
18.5.1 Summary of findings 387
19. Overall findings, discussion and recommendations 388
19.1 Introduction and research questions 388

19.2 Main findings 389
19.3 Discussion 390
19.4 Strengths and limitations of the study 395
19.5 Further research 399
19.6 Recommendations 401

Volume 3

Appendix 1 Mailout materials i
Appendix 2 Telephone questionnaire for non-participants ii
Appendix 3 Appointment confirmation package iii
Appendix 4 Postal questionnaire iv
Appendix 5 Medical Examination Data Collection Booklet v
Appendix 6 IMVS reference intervals and testing methodology vi
Appendix 7 Ethics Committees' Approvals x
References 403

Executive summary

Introduction

The Australian Gulf War Veterans' Health Study is the first comprehensive health study of a group of Australian War veterans involved in a single theatre of war. It has been conducted by a collaborative medical research team from the Department of Epidemiology & Preventive Medicine at Monash University, Health Services Australia Ltd, the University of Western Australia, and The Australian Centre for Posttraumatic Mental Health at the University of Melbourne.

A Scientific Advisory Committee, chaired by Professor Terry Dwyer, oversaw the study. A Consultative Forum, with representatives from several veteran and service bodies, was established to provide a link between the study team and the veteran and service communities. The membership of the Scientific Advisory Committee and Consultative Forum are detailed in chapter 5 of this report. The study was approved by the Ethics Committees of Monash University, the Department of Veterans' Affairs and the Department of Defence. The Ethics Committee of the Australian Institute of Health and Welfare oversaw approval of the cohort study of mortality and cancer.

This study was prompted by several factors. These include the results of several overseas studies, which had shown that the Gulf War veterans from coalition partner countries, such as the USA and UK, were reporting poorer than expected health. There was concern that some of the exposures and experiences unique to the Gulf War, such as the possible exposure to depleted uranium, chemical or biological weapons, anti-biological warfare medications, or smoke and oil from burning oil wells, may have resulted in health problems among Australian Gulf War veterans. In addition, there had been reports among Australian Gulf War veterans of a wide range of medical problems with no clear explanation.

Study aims

The Australian study was designed to investigate whether Australian Defence Force personnel who served in the Gulf War have a higher than expected rate of several adverse physical and psychological health effects and, if so, whether these effects are associated with exposures and experiences that occurred in the Gulf War. The specific research questions were:

1. Do Australian Gulf War veterans have an increased risk of psychological disorders including depression, anxiety and substance disorders and, if so, are these associated with exposures and experiences that occurred in the Gulf War?
2. Do Australian Gulf War veterans have increased prevalences of symptoms, symptom clusters and medical conditions, related to several body systems; in particular psychological, respiratory, neurological, musculoskeletal and skin and, if so, are these associated with exposures and experiences that occurred in the Gulf War?
3. Do Australian Gulf War veterans have an increased prevalence of chronic fatigue syndrome and, if so, is this associated with exposures and experiences that occurred in the Gulf War?
4. Do Australian Gulf War veterans have significantly poorer lung function than expected and, if so, is this associated with exposures and experiences that occurred in the Gulf War?

5. Do Australian Gulf War veterans have an increased prevalence of laboratory test results that are indicative of adverse health effects, including evidence of increased rates of markers of infection; and if so, are these associated with exposures and experiences that occurred in the Gulf War?
6. Do Australian Gulf War veterans have increased risk of having a child with a major congenital malformation, a child who later develops cancer or an increased risk of fertility difficulties, following return from the Gulf? If so, are these associated with exposures and experiences that occurred in the Gulf War?
7. Do Australian Gulf War veterans have increased rates of mortality and cancer?

Methods

The study compared the health of Gulf War veterans with that of a comparison group. The comparison group was randomly selected from members of the Australian Defence Force (ADF) who were eligible to be deployed to the Gulf War, but who were not deployed.

Attempts were made to contact all 1873 Gulf War veterans on the Gulf War Nominal Roll, and all selected comparison group members, to invite them to take part in the study. Subjects who could be contacted, and who gave informed consent to take part in the study, were asked to complete a lengthy postal questionnaire. This included several standardised questionnaires such as the Short-Form-12 Health Survey (SF-12) and the 12 item General Health Questionnaire (GHQ-12) and also contained questions about several aspects of physical, psychological and reproductive health, civilian occupational history, military and service history including all active deployments. Questions on Gulf War exposures and experiences included immunisations, medications against nerve gas agents, stressful military experiences, psychological stressors, smoke and oil clouds from the burning oil wells (SMOIL) and pesticides.

Participants were also asked to attend one of ten Health Services Australia medical clinics around Australia to undertake a comprehensive health assessment by teams comprising a doctor, nurse and psychologist, who were specifically trained for the study. The assessment included tests of lung function, skin testing for allergy, several blood tests, a fitness step test to assess fatigue, a full physical examination, more questionnaires relating to respiratory health and chronic fatigue, and an interviewer administered psychological assessment using the Composite International Diagnostic Interview (CIDI). All the blood samples were analysed at the Institute for Medical and Veterinary Science in Adelaide.

Recruitment, demographics and non-Gulf War exposures

At the end of recruitment in April 2002, 1456 Gulf War veterans had taken part, which was 80.5% of those eligible. Of the eligible members of the comparison group, 1588 took part (56.8%). More than 85% of participating Gulf War veterans and more than 70% of participating comparison group subjects were from the Navy, and approximately two thirds of participants were no longer serving members of the Australian Defence Force. There were very few women in either participating group, representing less than 2.5% of all participants. Therefore, in this report, the results are presented separately for male and female participants.

When the male Gulf War veterans were compared to the comparison group on several demographic, socioeconomic and lifestyle factors, the two groups were found to be very similar. There were some slight differences in relation to age, education and rank patterns, and pack years of smoking. Where applicable, subsequent health outcomes analyses were

statistically adjusted for these factors to ensure they were not the explanation for differences in health status found between the two groups.

Gulf War and other exposures

Gulf War veterans reported experiencing several chemical and environmental exposures, psychological stressors, immunisations and preventive medications in relation to the Gulf War. Amongst these, the most frequently reported exposures were typhoid and cholera immunisations; taking pyridostigmine bromide tablets (Nerve Agent Pre-treatment Set or NAPS); psychological stressors such as being in fear of death or injury, under threat of biological or chemical attack and being in a hostile environment; and chemical and environmental exposures such as solvents, fuel, dust storms, and the uncomfortable use of personal protective equipment.

Some exposures appear unique to the Gulf War military experience compared with other deployments or military activities, such as taking NAPS tablets and exposure to smoke and oil from burning oil wells (SMOIL). There were several exposures that veterans reported experiencing much more commonly during the Gulf War than during other deployments. These included possible exposure to depleted uranium, threat of chemical warfare and consequent use of protective clothing. These veterans also reported experiencing fearful situations more commonly during the Gulf War than during other military activities.

In relation to non-Gulf War exposures, male Gulf War veterans were a little more likely than the comparison group to have experienced one or more active deployments other than the Gulf War. Gulf War veterans and comparison group subjects who had been on other active deployments were similar in relation to the exposures and experiences reported for those non Gulf War deployments. The Gulf War veterans and the comparison group were also similar in relation to the exposures and experiences reported during other military activities and any civilian occupations.

Summary of health findings

The most striking and consistent health finding in the study was that the Gulf War veteran group had developed more psychological disorders than the comparison group in the time since the Gulf War. The Gulf War veterans were also more likely to have persisting psychological symptomatology in the twelve months or four weeks prior to the study. The greatest increase in risk was for posttraumatic stress disorder, but other anxiety disorders, depression and substance use disorders including problem drinking were also more common in the Gulf War group. Within the Gulf War veteran group, the risk of psychological disorders increased as the number of reported adverse military experiences related to the Gulf War increased. The increased risk of psychological disorders was only slightly reduced when Gulf War veterans were compared with comparison group subjects who had also been on an active deployment. The effect of Gulf War service on psychological health, therefore, can not be fully explained as representing a ‘deployment effect’.

Another major finding was that Gulf War veterans reported all of the general health symptoms more commonly than the comparison group. Further, Gulf War veterans were more likely to report a higher number of symptoms and to report symptoms that were more severe in nature. Neuropsychological and musculoskeletal symptoms were amongst the symptoms most commonly reported. When this increased symptom reporting was examined further using factor analysis to identify patterns of grouped symptoms, three groups of symptom “factors” were identified. They were groups of psychophysiological, cognitive and

arthro-neuro-muscular symptoms. However, these three groups of symptoms were very similar to the groups of symptoms found in the comparison group, suggesting that there was no unique pattern of symptom reporting in Gulf War veterans despite their higher rate of symptom reporting.

Gulf War veterans reported many medical conditions that had been diagnosed in 1991 or since (ie since the Gulf War) more commonly than the comparison group. The more commonly reported medical conditions in the Gulf War group related to back and other joint problems, skin and psychological disorders. When the reported medical conditions were restricted to those assessed by an HSA doctor as being 'probable' or 'possible' diagnoses, to improve the accuracy of diagnosis, the risks in the Gulf War veteran group remained elevated. Gulf War veterans were found to have a very low reporting rate of medical diagnoses, which were subsequently assessed as non-medical or unlikely, and similar rates as the comparison group, suggesting little over-reporting of these conditions by Gulf War veterans.

Self-perceived mental health status, as measured by the SF-12 and GHQ-12, was poorer in Gulf War veterans compared with the comparison group. Physical health status, again as measured by the SF-12, was also poorer however the difference between the two groups was not as marked. The reporting of health status by Gulf War veterans, according to other physical health indicators, was not consistently in the poorer direction. Gulf War veterans reported increased functional impairment but not increased current use of medication or increased hospitalisation. The groups were very similar on a range of physical health measurements, such as blood pressure, body mass index, waist-to-hip ratio and a fitness test.

The total number of symptoms reported, the physical and mental health measures using the SF-12 and functional impairment were associated in a similar pattern with several self-reported exposures that occurred in the Gulf War. These included 10 or more immunisations, stressful military service experiences, pyridostigmine bromide tablets, anti-biological warfare tablets, pesticides/insecticides and report of being in a chemical weapons area. General health symptoms, but not the SF-12 measures, were also associated with reported exposure to insect repellents. None of these health outcomes was associated with reported exposure to depleted uranium or to clusters of immunisations.

A wide range of laboratory investigations was undertaken. These included tests of the blood cells, function of the liver, function of the kidneys, biochemical indicators in the blood, measures of chronic inflammation and indicators of previous infections. While some of the Gulf War veterans' results were outside the expected range on many of these tests, a similar pattern was found in the comparison group. A greater proportion of Gulf War veterans had raised creatinine and sodium concentrations in the biochemical investigations, suggesting possible kidney disease, but the number of subjects affected was small and the clinical significance of this finding was uncertain. There was no unique pattern of blood test abnormalities in the Gulf War veteran group.

Gulf War veterans were more likely to report neuropathic symptoms than the comparison group but the medical examination of the neurological system, the findings of which were used to derived a 'neuropathy impairment score', showed little difference between the two study groups. However, analyses using combinations of neurological symptoms and medical examination findings were suggestive of an increased risk of a neuropathic disorder in Gulf War veterans. This is not able to be confirmed without further testing, such as nerve conduction studies. The reporting of neuropathic symptoms was associated with some

exposures that occurred in the Gulf War including immunisations, NAPS, antimalarials, solvents, repellents and pesticides.

Gulf War veterans were more likely than the comparison group to report respiratory symptoms, such as wheeze, cough, and shortness of breath, and wheeze was also a more common finding on physical examination in Gulf War veterans. Lung function testing using spirometry revealed no consistent differences between the two groups. In Gulf War veterans, no consistent association was found between abnormal respiratory health and reported exposure to the smoke and oil from the burning oil wells.

Gulf War veterans reported, or were assessed as having, all fatigue-related health outcomes more commonly than the comparison group. Chronic fatigue syndrome was defined using a recognised set of criteria for this condition. Eleven of the Gulf War veterans and only two of the comparison group met this definition. While this finding demonstrated an excess risk of developing chronic fatigue syndrome in Gulf War veterans, the numbers were too small to explore possible associated exposure factors. There was one minor difference in the immunological profile of Gulf War veterans compared with the comparison group subjects with chronic fatigue syndrome; the clinical implication of which is of uncertain significance.

Gulf War veterans were more likely than the comparison group to report difficulties with fertility following the period of the Gulf War. However, veterans with these difficulties were more likely than the comparison group to subsequently father a successful pregnancy. In the period since the Gulf War, Gulf War veterans were no more likely than the comparison group to father a pregnancy that resulted in a miscarriage, stillbirth or termination. In addition, for the live births since the Gulf War, rates of low birth weight, prematurity, reported birth defect, cancer or reported death in the children were similar for the two groups.

The mortality and cancer experience of the two groups since the time of the Gulf War was examined by matching the names against the national death and cancer registries. The numbers of deaths and cancers were small and the death and cancer rates for each group were lower than those expected in the general Australian population. When the Gulf War and comparison groups were compared with each other, there was a small excess of disease related deaths in the Gulf War group, but the numbers are too small at this stage to draw any meaningful conclusions from this. Deaths due to accident were similar in the two groups.

The health of female Gulf War veterans was considered separately from the male veterans. This was because the number of female Gulf War veterans was considerably smaller than the male veterans and health patterns in males and females differ. Of the 38 female Gulf War veterans, 32 (84.2%) took part in the study, as well as 40 of 73 (54.8%) female comparison group subjects.

Unlike male veterans, female Gulf War veterans only reported about half of the general health symptoms more commonly than the female comparison group. However, the more commonly reported symptoms, such as fatigue, headaches and irritability, were similar to those more commonly reported by their male counterparts. Of the reported medical conditions, psychological disorders were generally the conditions reported more commonly by female Gulf War veterans than by the comparison group, a similar pattern to that found in the male veterans. Female Gulf War veterans had poorer self-reported mental health, as measured using the SF-12 and the GHQ-12, than the comparison group, but were similar on the SF-12 physical health measure. Again, this was a similar pattern to that found in male participants. Female Gulf War veterans were more likely to have a CIDI diagnosed psychological disorder that was present within the previous 12 months, but were no more

likely to have a psychological disorder that was first present in the post-Gulf War period than the comparison group. Reported asthma was a little more common in the Gulf War group, but all other indicators of respiratory health were similar. No differences were found for blood pressure, body mass index, results of blood tests, neurological health, chronic fatigue syndrome or reproductive outcomes. Using the national registry searches, no female Gulf War veterans were found to have died while one was found to have developed cancer during the period of the cohort study.

Therefore, in response to the main hypothesis of the study we conclude that the psychological health and some aspects of physical health of Australian veterans of the Gulf War do differ significantly from similar Australian Defence Force personnel who were not deployed to the Gulf War. The differences in physical health primarily relate to self-reported symptoms and medical conditions rather than more objective measures of physical health.

Increased symptom reporting, increased medical condition reporting and poorer perception of health may be early indicators of more serious health outcomes occurring in the future. Increased psychological health abnormalities have also been shown to lead on to later physical health problems. The only way to assess longer term sequelae this would be to do a follow-up health study in the future, to enable comparisons to be made with the baseline data collected as part of the current study. Follow up matching studies will be needed to adequately assess rates of cancer and causes of death, as the numbers are too small at this stage to be able to investigate this in a meaningful way. Follow–up of other health disorders found in excess in Gulf War veterans, such as posttraumatic stress disorder, would be useful to document longer term outcomes of such conditions.

The analysis has also identified health outcomes, which were common in both groups and may relate to ADF service in general, and not just the Gulf War. These outcomes include musculoskeletal disorders, high body mass index and high rates of alcohol use. Therefore, the dataset and the subjects in the two groups who have taken part in the study should be seen as a unique resource, which could be used to further investigate such health patterns in ADF personnel, including veterans of other deployments. These were beyond the scope of the research questions for the present study, as they would not just relate to Gulf War service.

Strengths and limitations of the study

There were several strengths of this study when compared with previous studies. Firstly, it included a comparison group, which was very similar on many characteristics that are predictive of health status, such as age and smoking status. This meant that these characteristics were unlikely to explain any differences in health between the two groups. Secondly, during the analysis we considered the effect that a lower participation rate in the comparison group may have had on our assessment of risk using two different but complementary methodological approaches. This determined that, while participation bias could not be excluded, it was unlikely to explain large differences found. A third strength was that we collected a large amount of information on exposures to allow us to explore the relationship between specific aspects of Gulf War service and health. Fourthly, we included several objective tests of health, rather than relying solely on self-reports of health from the participants themselves, which had been the main focus of many previous studies.

Another strength for this large, multidimensional study was having a large group of senior investigators with diverse expertise across a range of health research areas. In addition, the research was undertaken in a strong research environment by a study team which remained together over the almost three years of the study. This was complemented by the input of

HSA, which was able to ensure consistency in data collection through its network of health clinics throughout Australia. The study team met regularly with the Scientific Advisory Committee and Consultative Forum over the planning, data collection, analysis and reporting phases of the study.

There were however, some limitations to the study, which we were able to address to some extent. It needs to be noted that this was a cross-sectional survey undertaken at one point in time more than ten years after the Gulf War. Therefore, it is difficult to attribute the excesses in health problems with absolute certainty to this past period in the veterans' lives. Nevertheless, the inclusion of a comparison group drawn from the ranks of the ADF at the same time as the Gulf War does help to give more weight to the conclusions.

Secondly, much of the health and exposure information was reported by the veterans themselves, relying on their memory of events many years in the past, and these may not always be accurate or able to be validated. This can result in a form of recall bias, where the Gulf War veterans are more likely then the comparison group to date health outcomes to the time of the Gulf War. To address this, we undertook a validation of the reported medical diagnoses and found that the higher rates of these validated conditions in Gulf War veterans tended to persist. The level of inaccurate reporting was low, and at similar levels to that in the comparison group, suggesting that over-reporting was not a major factor. This type of validation could not be done for other health outcomes.

A third potential problem was that there were very many analyses undertaken for this study. This increases the likelihood that some apparent excesses in health risks may be found due to chance alone. To address this problem, we have tended to emphasise those findings where consistent patterns have been shown in different analyses, where these confirm similar findings in previous studies, or where there is a biologically plausible reason for the finding.

In summary, the study design for the Australian Gulf War Veterans' Health Study had several strengths over many previous studies of Gulf War veterans, which has allowed us to investigate more health outcomes, and to better assess the possible effects of Gulf War experiences and exposures. There are inevitable limitations in this type of study, but we were able to anticipate many of these and build into the study design and analysis several measures to reduce the impact of these factors. Nevertheless, factors such as participation bias and recall bias cannot be completely excluded as at least partly explaining some of the findings.

Recommendations

While the main focus of this report has been to document the study findings in relation to the health of Gulf War veterans, we have also formulated a few key recommendations in relation to communication of the study findings, application of the findings, possible avenues for further research and measures to make such studies easier to undertake in the future. These recommendations, with some explanatory notes, are:

1. **There should be wide promotion of the study findings to the veteran and service communities, the Departments of Defence and Veterans' Affairs, the Repatriation Commission, ADF Medical Officers, the broader Australian community and the scientific community.**
   The findings of this study are likely to be important factors in diagnosis and management of Gulf War veterans and in consideration of entitlements for these veterans.
2. **Consideration should be given to measures to reduce adverse psychological impacts of military service or deployment related activities on Defence Force personnel, especially in relation to better psychological preparation for the possibility of**

chemical or biological weapons attack.
Such weapons are likely to remain a threat in future conflicts. Having a deployed or deployable force which is psychologically better prepared, as well as more reliable systems for monitoring whether biological or chemical attack have in fact occurred, may assist in reducing the fear associated with the threat of such attack and subsequent psychological morbidity.

3. **Consideration should be given to developing a minimum health dataset collected routinely in a standardised manner on all individuals before active deployments**.
Health status information for Gulf War veterans, which predated the Gulf War or was collected routinely at the time of deployment, would have provided extremely useful baseline data against which the health of veterans could later be compared.

4. **Consideration should be given to developing procedures for more accurately documenting exposures during active deployments**.
One of the difficulties for our study was the paucity of accessible, well documented exposure data from the time of the Gulf War. This includes information on immunisations and preventive medications, such as pyridostigmine bromide.

5. **Consideration should be given to the further development, including validation, of the Military Service Experience questionnaire for use in practice to assess the effect of deployments and in future studies.**
This questionnaire could become a standard measure of deployment-related stressors for ADF personnel, to be used as a predictor for psychological health outcomes and in any future psychological health intervention studies.

6. **Consideration should be given to undertaking further analyses of the dataset and/or collecting further data to address other questions raised about the impact of Gulf War service, or other aspects of military service, on health.**
The data collected during this study is a unique resource, which could be further analysed to answer further questions in relation to the effects of Gulf War service, other deployments and other aspects of military service on health outcomes, especially where there were problems of small numbers or poor data quality. Examples are immunisations and chronic fatigue. This could be supplemented by further data collection for some health outcomes, such as peripheral neuropathy, which the study was not able to adequately address.

7. **Consideration should be given to undertaking follow-up studies, especially in relation to the cohort mortality and cancer study, but also in relation to some of the health outcomes found in excess in Gulf War veterans, such as posttraumatic stress disorder.**
The mortality and cancer study will only start to provide useful data to investigate causes of death and different types of cancer as the cohort ages. Follow-up studies for other health outcomes, such as posttraumatic stress disorder, skin disorders and symptom reporting, found in excess in Gulf War veterans, will document the longer term outcome of these effects.

8. **A Board of Trustees should be appointed by the Repatriation Commission for the purpose of governing future access to the serum held in long-term storage.**
The Board of Trustees should consist of members representing Monash University, the Department of Veterans' Affairs and the veteran community.

Acknowledgments

We would like to gratefully acknowledge the contribution of several individuals and groups who have assisted us in undertaking the Australian Gulf War Veterans' Health Study. A large multidisciplinary study such as this requires input from people from very diverse disciplines and backgrounds from both the research and veteran communities.

We are grateful to the following Australian-based researchers for their assistance with particular aspects of the study design, data collection instruments and analysis: Prof Ian Hickie and A/Prof Andrew Lloyd, University of NSW, Sydney, NSW; Prof Christopher Fairley, University of Melbourne; Dr Jane Halliday, Perinatal Data Collection Unit, Department of Human Services, Victoria; A/Prof Paul Lancaster, National Perinatal Statistics Unit, Australian Institute of Health and Welfare; Dr Wendy D'Souza and Dr Richard Macdonell neurologists, Austin & Repatriation Medical Centre; Captain John Parkes, CSC, RANR retired; A/Prof Andrew Mackinnon, Mental Health Research Unit of Victoria and Department of Psychological Medicine, Monash University; Dr David Johns, Department of Respiratory Medicine, Alfred Hospital; Dr Krystyna Rowland, pathologist, Institute of Medical and Veterinary Science; and Mr Bill King, Centre for Tobacco Control, Cancer Council of Victoria.

There are several international researchers who we would like to thank for their assistance and advice. We would particularly like to thank Prof Simon Wessely and Ms Catherine Unwin of the Gulf War Illness Research Unit, Guy's, King's and St Thomas's Medical School, London, UK; Dr Han Kang, Department of Veterans Affairs, Washington DC, USA; Dr Craig Hyams, Epidemiology Division, Naval Medical Research Institute, Maryland, USA; Col K.C. Scott, National Defence, Canada; Dr Bradley Doebbeling, The Iowa Persian Gulf Study Group, University of Iowa, Iowa, USA; Dr Drue Barrett, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; and Prof Nicola Cherry, previously at University of Manchester, UK; and Group Captain William Coker, Royal Air Force, UK. We are particularly grateful to those researchers in this group who have allowed us to use parts of their questionnaires and other data forms.

There are also many other people who have provided important input to the study. These include the Gulf War veterans in the focus group who assisted in the development of the Military Service experience questionnaire; Dr Keith Horsley and Dr Warren Harrex of the Department of Veterans' Affairs (DVA); Mr Bob Connolly and his contact and recruitment team at DVA; Dr Phil Boorman, DVA; the Scientific Advisory Committee chaired by Professor Terry Dwyer OA, Menzies Centre for Population Health Research, University of Tasmania; Dr David Stevens, the Director of Naval Historical Studies; Roger Lee, Army Historian; Mr Dave Watts, Cdre Michael Dowsett and the other members of the Consultative Forum; the Personnel Branches of the Navy, Army and Air Force and the many other serving and former members of the Australian Defence Force who provided advice and information.

Dr Michael Pincus was the National Projects' Coordinator for HSA at the commencement of the study. Dr Pincus very unfortunately became seriously ill and died during the course of the study. We would like to gratefully acknowledge Dr Pincus' strong support for this study and his very important role in the early development and conduct of the study methods. We would also like to acknowledge the HSA team which included administrative staff, nurses, doctors and clinical psychologists who provided the medical and psychological assessments for the study. These were the data collectors who actually liaised with, interviewed and examined all the Gulf War and comparison group participants in the study.

The authors acknowledge the help provided by several other members of the Monash University team in setting up and ensuring the smooth running of the study; Ewan MacFarlane, Geoff Aldred, Koraly Giuliano, Emma Conyers, Julie Attard, Jane Ball and Lucia MacFarlane.

Finally, and very importantly, we would like to acknowledge the time and effort made by Gulf War veterans and members of the comparison group to participate in this study. They freely gave up their time to make a very important contribution to health research of Australian veterans.

List of abbreviations

AACB	Australasian Association of Clinical Biochemists
Ab	Antibodies
ABWT	Anti-biological warfare tablets
ACGIH	American Conference of Governmental Industrial Hygienists
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACT	Australian Capital Territory
ADF	Australian Defence Force
AFFA	Armed Forces Federation of Australia
AGWVA	Australian Gulf War Veterans Association
AIDS	Acquired immune deficiency syndrome
AIHW	Australian Institute of Health and Welfare
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AS/NZS	Australian Standards/New Zealand Standards
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUDIT	Alcohol Use Disorders Identification Test
AVADSC	Australian Veterans and Defence Services Council
BMI	Body mass index
BTPS	Body temperature and pressure
BTX	Benzene, toluene and xylene
C	Celsius
C&E	Chemical and Environmental (exposures)
CARC	Chemical Agent Resistant Compound paint
CBE	Complete blood examination
CCEP	Comprehensive Clinical Evaluation Program
CDC	Centers for Disease Control and Prevention, Atlanta, Georgia, USA

CDn	Subsets of T cell lymphocytes
CDT	Clearance Diving Team
CES	Combat Exposure Scale
CFS	Chronic Fatigue Syndrome
CG	Comparison Group
CHD	Coronary heart disease
CHPPM	US Army Center for Health Promotion and Preventive Medicine
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CIWS	Close in weapons system
CMV	Cytomegalovirus
CNS	Central nervous system
CO	Carbon monoxide
CO_2	Carbon dioxide
Comp grp	Comparison group
CRP	C-reactive protein
DEET	N,N-diethyl toluamide, an insect repellent
DNA	Deoxyribonucleic acid
DoD	Department of Defence (US)
DSM-III-R	Diagnosis of Statistical and Mental Disorders, 3rd edition, revised
DSM-IV	Diagnosis of Statistical and Mental Disorders, 4th edition
DU	Depleted Uranium
DVA	Department of Veterans' Affairs
EBV	Epstein Barr virus
ECCS	European Community Coal and Steel
ECRHS	European Community Respiratory Health Survey
EPA	Environmental Protection Agency
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration (USA)
FEV_1	Forced expiratory volume in one second

FT	Full time
FVC	Forced vital capacity
GGT	Gamma-glutamyl-transferase
GHQ-12	General Health Questionnaire-12 item
GW	Gulf War
GWV	Gulf War veteran
H_2S	Hydrogen sulphide
Hb	Haemoglobin
Hep C	Hepatitis C serology
HIC	Health Insurance Commission
HMAS	Her Majesty's Australian Ship
HSA	Health Services Australia
ICD-10	International Classification of Diseases, 10^{th} revision
ICD-9	International Classification of Diseases, 9^{th} revision
ICD-0-2	International Classification of Diseases - Oncology, 2^{nd} edition
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IMVS	Institute of Medical and Veterinary Science
ISO	International Standards Organisation
ISWA	Incapacitated Servicemen and Women's Association of Australia Inc.
LFT	Liver function tests
LSE	Logistic Support Element
MATU	Mobile Air Terminal Unit
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MEPA	Saudi Arabian Meteorology and Environmental Protection Administration
MFO	Multinational force and observers
MIMS	Monthly Index of Medical Specialties
MMR	Measles, mumps, rubella (immunisation)

MRR	Mortality rate ratio
MSE	Military Service Experience
n	Number
NAAQS	National Ambient Air Quality Standards (US)
NAPS	Nerve Agent Pre-treatment Set
NATA	National Association of Testing Authorities, Australia
NBC	Nuclear, chemical and biological protective clothing
NGWV	Non-Gulf War Veteran
NHMRC	National Health and Medical Research Council
NIDDM	non-insulin-dependent diabetes mellitus
NIOSH	National Institute of Occupational Safety and Heath
NK	Natural Killer (cells)
NO_x	Nitrogen oxides
NSMHWB	National Survey of Mental Health and Wellbeing
NSW	New South Wales
NT	Northern Territory
OP	Organophosphate, a type of pesticide
OPIDPN	Organophosphate-induced delayed polyneuropathy
OR	Odds ratio
p-value	Probability value
PAH	Polycyclic aromatic hydrocarbons
PB	Pyridostigmine bromide (in NAPS tablets)
PCL-S	Posttraumatic Stress Disorder Checklist – S
PCP	Phencyclidines
PCV	Packed cell volume
PM_{10}	Inspirable particulate with an aerodynamic diameter less than 10 microns
ppb	Parts per billion
ppm	Parts per million
PT	Part time
PTSD	Posttraumatic stress disorder

QLD	Queensland
R&R	Rest and recreation
RAAF	Royal Australian Air Force
RAF	Royal Air Force (UK)
RAN	Royal Australian Navy
RAST	Radioallergosorbent test
RCC	Red cell count
RCPA	The Royal College of Pathologists of Australasia
RDFWA	Regular Defence Force Welfare Association
RN	Royal Navy (UK)
RPE	Respiratory protective equipment
RR	Relative Risk
RSL	Returned and Services League of Australia Limited
SA	South Australia
SAC	Scientific Advisory Committee
SCUD	Soviet short-range surface-to-surface missile
SD	Standard Deviation
SF-12	Short-Form-12 Health Survey
SF-36	Short-Form-36 Health Survey
SIR	Standardised Incidence Ratio
SMOIL	Smoke from oil well fires
SMR	Standardised mortality ratio
SOx	Sulphur oxides
SRR	Standardised Risk Ratio
SVOC	Semi-volatile organic compounds
TFT	Thyroid function tests
TGMSE	Task Group Medical Support Elements
TLV	Threshold Limit Value
TPI	Total and Permanently Incapacitated Association
TSH	Thyroid stimulating hormone

TSI	Torres Strait Islander
TSP	Total suspended particulate
U	Uranium
U & E	Urea and electrolytes
U/L	Units per litre
UK	United Kingdom
UN	United Nations
UNSCOM	United Nations Special Commission
UNTSO	United Nations Truce Supervision Organisation
US	United States (of America)
USA	United States of America
USAEHA	United States Army Environmental Hygiene Agency
USIAAT	US Interagency Air Quality Assessment Team
USNS	United States Naval Ship
USS	United States Ship
VA	Veterans Affairs (US Department of)
VIC	Victoria
VO_2	Maximum oxygen uptake
VOC	Volatile organic compound
WA	Western Australia
WCC	White cell count
WHR	Waist to hip ratio
WMO	World Meteorological Organisation
WWII	World War II

1. Introduction

Iraq invaded Kuwait on August 2, 1990. In response, Australia provided military forces to the Gulf area in support of United Nations Security Resolutions as part of a larger multinational response. These Australian deployments are defined as operational service for the purposes of the Veteran's Entitlements Act 1986.

Following the Gulf War, defence personnel from several countries that had deployed troops began to report a wide range of health complaints. In response, there has been a sustained effort internationally to investigate the health of Gulf War veterans, with studies having been conducted of Gulf War veterans from the United States of America, Great Britain, Canada and Denmark. While some health problems were found to be more common among these Gulf War veterans, this field of research has had many limitations. These limitations have included health outcome data based mainly on self-report, self-referred populations in registry studies, problems in objectively measuring exposures and difficulties contacting study participants with resultant low response rates, particularly for control groups. Prior to this study, there has been no systematic study of the health of Australian Gulf War veterans.

Most of the published health studies have been of Army Gulf War veterans from the UK and USA. They have therefore tended to focus on health outcomes and exposures of Army veterans, rather than those of veterans in the Navy or Air Force. As over 90% of the Australian Gulf War veterans were in the Navy, the exposures and experiences of Australian Gulf War veterans were likely to be different from those of their international counterparts from the UK and USA. Therefore, the results of published overseas studies may not be relevant or generalisable to Australian Gulf War veterans.

There has been increasing interest among the Australian Gulf War veteran community in a study of Australian Gulf War veterans. In light of this, the limitations of overseas studies and the different service experience of the Australian Defence Force in the Gulf, it was decided to undertake a study to investigate in a comprehensive way the health of Australia's Gulf War veterans. Through an open tender process, research groups were invited in December 1999 to submit proposals to undertake this study. The Department of Epidemiology & Preventive Medicine at Monash University, in collaboration with Health Services Australia, was selected by the Department of Veterans' Affairs to conduct an independent study of the health of Australian Gulf War veterans on behalf of the Commonwealth Departments of Veterans' Affairs and Defence. The study was funded by the Department of Veterans' Affairs. In addition, a Scientific Advisory Committee was established to oversee the conduct of the study and a Consultative Forum was set up to represent the veteran community and in turn feed back information about the study to its constituent members.

This report outlines the background to the study, aims and objectives, methods used to assess health outcomes and relevant exposures, results of the study, discussion, conclusions and recommendations. It also contains an Executive Summary.

2. Australian involvement in the Gulf War

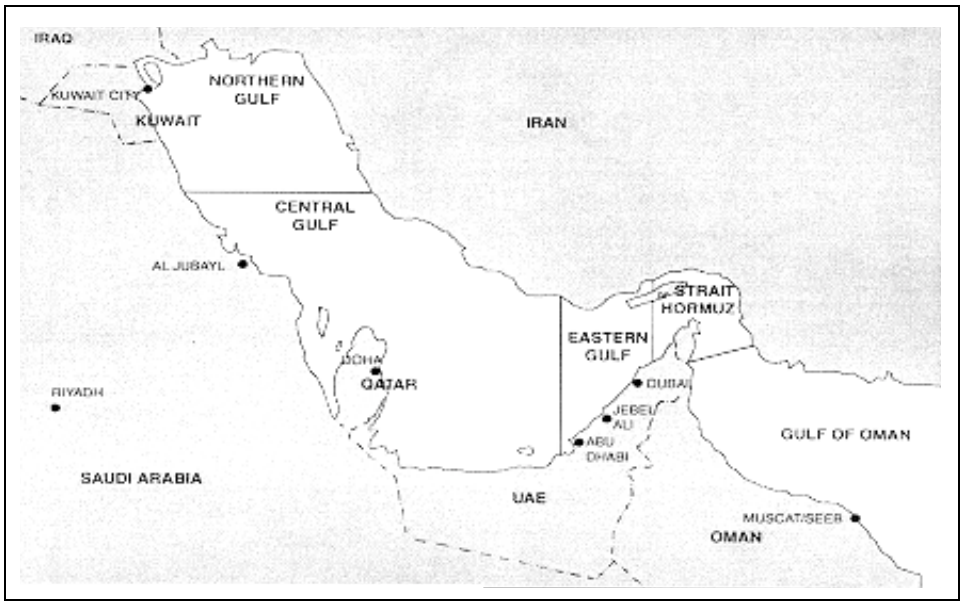
This chapter is not meant to be a comprehensive or definitive account of Australia's Gulf War involvement, rather it covers the information of most relevance to the study and more comprehensive details can be found in other literature.[1-8]

The timelines for the Australian deployments are presented in Figure 2.2. and in Table 2.1. These Australian deployments are defined as operational service for the purposes of the Veteran's Entitlements Act 1986.

2.1 The Gulf Region

Kuwait occupies an area of only 17,818 square kilometres. It borders the Gulf and has a well-sheltered harbour free of sandbanks. Annual rainfall varies from one centimetre (cm) to 37 cm, occurring usually between November and April. The coolest month is January, when temperatures range between – 2.8° Celsius (C) and 28.3°C. During the months June to August (the Northern Hemisphere summer) the shade temperature can reach 49°C. The land is flat desert, with few oases and little drinking water. Most water supplies are piped from the Shatt al-Arab waterway after being desalinated. The Shatt al-Arab is the confluence of the Tigris and Euphrates rivers, and flows into the Gulf at Kuwait. Kuwait's main industry is oil and it possesses 2.6 per cent of the world's oil supplies.[7]

Figure 2.1 Map of the Gulf region



2.2 Australian Deployment in the Gulf War

The Gulf War commenced on 2 August 1990, when Iraq invaded Kuwait, and the formal ceasefire was announced by the United Nations on 12th April 1991.[9] Following an announcement on 10th August 1990 by the Prime Minister, Australia provided a naval task force to the Gulf area as part of a larger multinational response to Iraq's invasion of Kuwait, in support of United Nations Security Resolutions.[7] There were several different deployments. Most primarily involved Royal Australian Navy (RAN) personnel, and these included personnel on Her Majesty's Australian Ship (HMAS) *Darwin*, HMAS *Adelaide* and

HMAS *Success* deployed in Operation Damask I; HMAS *Brisbane*, HMAS *Sydney* and HMAS *Westralia* deployed in Operation Damask II; HMAS *Darwin* deployed in Operation Damask III; Clearance Diving Team 3; and Task Group Medical Support Element (TGMSE) deployed to USNS *Comfort*. Female Australian Defence Force (ADF) personnel served on HMAS *Westralia*, in Operation Habitat and in the TGMSEs deployed on USNS *Comfort*.

The Royal Australian Air Force supplied transport and logistic support but did not fly combat missions. Other ADF personnel who were involved in Gulf operations included intelligence officers (mainly Air Force but some Navy and Army) and Army linguists. Some individual officers (mainly Army) were on secondment to United Kingdom (UK) and United States of America (USA) forces and deployed to the region with those forces.[6, 7]

Other ADF deployments in the region at this time included Operation Habitat and Operation Blazer. Personnel from these operations are included in the study.

2.2.1 Damask I

On 22nd August 1990, ships of the task force left Australia for the Gulf region, to take part in the blockade of the Gulf of Oman. The deployment was in response to the UN Security Council Resolution 661 imposing economic sanctions on Iraq that had been passed on 6th August.[7] The deployment consisted of the guided missile frigates HMAS *Adelaide* and HMAS *Darwin*, accompanied by HMAS *Success*, a replenishment ship. Five Navy Fleet Air Arm Seahawk and Squirrel helicopters were assigned to the ships.[7] *Success* had eight Army personnel assigned from the Air Defence Regiment and was equipped with a Bofors Robotic System 70 missile system. *Darwin* and *Adelaide* were equipped with anti-aircraft, anti-surface missiles, torpedo tubes and each had a Phalanx Close-in-Weapon-System (CIWS). *Darwin* had an Army linguist assigned for the deployment.[6]

When the Australian ships in Damask I arrived in the Gulf of Oman on 6th September, towards the end of the northern hemisphere summer, salt and dust haze had reduced visibility.[2] Temperatures were in the high 30s.[7] *Darwin* and *Adelaide* were deployed east of the Straits of Hormuz only. Both of the frigates were involved in firing warning shots across the bows of potentially hostile ships and then boarding and searching them.[1, 2] The frigates challenged hundreds of ships, were involved in several major visit and search operations and sank several floating objects.[1, 2] *Success* also challenged ships and completed 219 replenishments of coalition ships.

Chemical alarms sounded several times on *Darwin* although each sounding was quickly identified as a false alarm.[2] There were a number of fire alarms on *Success* which were also identified as false alarms.[3] During Damask I, Iran's attitude to the ships taking part in the blockade was unknown and this added to the stress of the deployment. On 7th September, *Darwin* was overflown by an Iranian P3 which came to within three nautical miles of the ship.[2] HMAS *Success* was also overflown by an Iranian P3 on the 12th October.[3]

Darwin and *Adelaide* left the area of operations to return to Australia on 3rd December 1990 before coalition air strikes and the ground war began. *Success* left the area on the 23rd January, after the coalition air strikes had started but just before the ground war.[6]

2.2.2 Damask II

The second task group took over sanction enforcement duties from Damask I in December 1990. Damask II included the guided missile destroyer HMAS *Brisbane*, the guided missile frigate HMAS *Sydney*, helicopters, three Army linguists and the supply ship HMAS

Westralia with four Army personnel assigned from the Air Defence Regiment to man the Bofors Robotic System 70 missile system. *Brisbane* was equipped with guns, a missile system, high definition radar and two Phalanx CIWS. *Sydney* was equipped with the same weapons as the two other frigates *Adelaide* and *Darwin* (section 2.2.1). *Westralia* is a petroleum product tanker modified for use as a replenisher at sea.

Brisbane and *Sydney* reached the Gulf of Oman on 3rd December 1990. In mid December *Success, Brisbane* and *Sydney* went through the Straits of Hormuz, to the central Gulf, to enforce sanctions. *Westralia* replaced *Success*, as the supply ship, on 26th January during the ground war. From the start of the coalition air strikes on 17th January, *Brisbane* and *Sydney* acted as anti-aircraft warfare pickets and defended the US aircraft carrier Midway.[4, 5] *Brisbane* controlled air traffic and *Sydney* contributed to the anti-aircraft screen.[7]

It was thought highly likely that Iraq would launch a pre-emptive attack and there were several feints by Iraqi combat aircraft.[9] A high level of vigilance was maintained and combat training including chemical defences were practised.[9] In late December the Iraqis released contact mines into the Gulf.[9]

A Red air and surface and air warning was issued on 17th January.[4] On the 24th January, there was a Red air warning in HMAS *Sydney*, the ship's log also recorded air attacks to the north and a flash to the southeast. Mines and mine-like objects were seen in the Gulf where the ships were operating in February and March.[4]

In mid February *Sydney* moved close to Kuwait to search for and recover allied pilots forced to eject.[9] By 23rd February, *Sydney*'s Seahawk was checking Kuwaiti islands and drilling platforms for Iraqi troops, observation posts and gun emplacements.[7] The ceasefire on 28th February reduced the threat of air strikes but floating mines continued to be a threat .[9] On the 12th of March SMOIL is recorded to the north east in the Ships' log and on the 23rd March *Sydney* was overflown by an Iranian P3C.[4] *Sydney* was in a severe dust storm on 7th March 1991 which caused sea searches and mine searches to be cancelled.[4]

Brisbane and *Sydney* left the Gulf on 26th March 1991. *Westralia* left 2 months later on 28th May having completed 90 replenishments; refuelling ships from 11 nations.[6, 8] There were a number of false alarms from the Minerva system on board *Westralia* and the ship also experienced a small fire in the engine room on 19th July.

2.2.3 Damask III

On 13th June 1991, HMAS *Darwin* arrived in the Gulf for its second deployment. It carried out sea and air surveillance and escorted US aircraft carriers and merchant ships through mine cleared areas. Smoke, oil and dust clouds from burning oil wells (SMOIL) was reported in the ship's logs on several occasions between 25th June and 10th August and a dust storm was reported on 17th July. It left the Gulf on 4th September 1991.[2]

2.2.4 Clearance Diving Team 3

A Clearance Diving Team (CDT) consisting of 23 personnel left Australia on 27th January 1991, and arrived in Muscat on 31st January. While in Bahrain the team laid a portable degaussing range in the ship repair yard. A reconnaissance party from the CDT arrived in Kuwait on 5th March via Saudi Arabia. This team took Australia's only Iraqi prisoner during reconnaissance of Doha port, west of Kuwait City. Because of the sabotage of the Kuwaiti oil wells by the Iraqis, the team worked in a thick oil slick at Mina Ash Shuibah, the deep water port south of the city. This resulted in difficulty with visibility and required extensive

cleaning of equipment after use. Approximately 400 miles of the Gulf shoreline was oiled[10] but Kuwait city (Ras al Shuwaik) was reported to be relatively free of oil.

The team lived and worked against a background of black smoke (SMOIL) from the burning oil wells. They also operated under time pressure to open the harbour for humanitarian relief supplies and to land heavy equipment. After clearing Mina Ash Shuibah the team went on to clear the Naval base and then Kuwait City's port. By this time, atmospheric conditions had improved and the sun had made its first clear appearance for two weeks. Some team members worked at Mina Ahmadi, the oil terminal, where atmospheric pollution was worse than in Kuwait city. The atmosphere was so bad that operations had to be cancelled on 16th March. Members of the team were also involved in various shore-based tasks, including recovery of missiles and small arms from "Death Valley". The team found bodies of four Iraqi swimmers off shore, human remains were also found in ships that were surveyed. The team laid over 200 Jackstays, rendered 30 demolition charges safe, dealt with 60 sea mines, cleared over 230,000 pieces of ordnance including silkworm missiles and cleared seven ships and many buildings. By 19th April the team had completed the task of clearing the Kuwaiti coastline. The team returned to Australia on 10th May.[6]

2.2.5 Task Group Medical Support Elements on USNS *Comfort*

The Australian Defence Force raised the Task Group Medical Support Elements under RAN medical command as a contribution to the coalition medical support requirement. The TGMSE's were assigned to the American hospital ship USNS *Comfort*. TGMSE 1 was composed of 20 members comprising doctors, nurses and health administration personnel, predominantly Navy supplemented with Army and Air Force personnel, including members of the Reserve forces. TGMSE 1 assumed duty on the 13th September 1990 and completed service on 4th January 1991. TGMSE 2 were deployed 31st December and TGMSE 3 on 13th January, the two later Elements remaining until 15th March 1991, after the ground war. A total of 59 Australian servicemen and women participated in this effort.[11]

USNS *Comfort* remained on task in the Gulf following the ship's arrival in September 1990, except for one brief period in the Gulf of Oman. Comfort was based at Bahrain, but spent the majority of the time undertaking duty to the north in Gulf waters. The Australian TGMSE personnel undertook normal medical duties and participated in operational medical exercises and drills including training for the handling of casualties of biological and chemical warfare. Although large numbers of casualties did not occur, medical personnel were required to manage seriously injured and ill personnel including gunshot wounds and the mortally injured casualties from the explosion on USS Iwo Jima. The mechanical failure of air conditioning plant on USNS *Comfort* resulted in TGMSE members experiencing extremes of temperature and humidity below decks for several days (Kerry Delaney personal communication).

On 26th February the ship sailed to Khafji on the border between Kuwait and Saudi Arabia. At this time, there were 2-3 weeks when the sky was darkened with SMOIL, visibility was reduced to less than 70 metres and personnel wore surgical masks for protection when on deck because the ship was enveloped in thick black smog (personal communication ADF personnel). *Comfort* was located between Iraq and Dahran when a sustained SCUD missile attack resulted in 29 US fatalities.[11] There was a report that USNS *Comfort* was targeted by a silkworm missile although hospital ships were afforded protection by screening frigates.[11] A number of ships were damaged as a result of mines and one such mine was disabled ahead of *Comfort* on 4th March.[11]

The Australian doctor in Command of TGMSE 2 and 3 ordered personnel not to take anti-malarials or Nerve Agent Pre-treatment Set (NAPS) tablets after consultation with senior US Navy colleagues (personal communication ADF personnel).

2.2.6 Operation Habitat

Operation Habitat was deployed to Kurdistan in northern Iraq on 16th May 1991. The Operation, comprising approximately 75 ADF personnel, provided humanitarian support to the international relief effort for Kurdish refugees. Personnel were primarily Army with a few Air Force members. Operation Habitat included medical, dental and preventive health teams.

The medical teams treated 2766 Kurds and the dental team treated 265 Kurds. The preventive medical team conducted health surveys, water and bacteriological testing and undertook pest control and fumigation programmes.[6] The Operation Habitat personnel lived in tented accommodation but were supplied with food via the British Supply Chain in operation for UK Operation Safe Haven. Some of the personnel passed through Kurdish villages destroyed by the Iraqis possibly by chemical warfare (personal communication ADF personnel). The mission was completed on 30th June when the teams left for Australia.[6]

2.2.7 The United Nations Special Commission (UNSCOM)

Australia sent five members of the ADF to support Operation Blazer in March 1991, to oversee the identification and destruction of the Iraqi weapons of mass destruction. Over a period of some years, members of UNSCOM visited suspected Iraqi chemical and biological weapons manufacturing and storage facilitates. They discovered that such weapons had been made and stored by the Iraqis at several sites and in the process of discovery, they may have been exposed to chemical and biological warfare agents. Two other members of the ADF were part of the UNSCOM International Atomic Energy Agency Inspection Team.

2.2.8 Summary of ADF Deployments

The ADF deployed 1871 personnel to the Gulf according to the Nominal Roll for the Gulf War. There were no Australian deaths during the war.[7] It was public knowledge that Iraq had stockpiled chemical and/or biological weapons. ADF personnel were concerned that Iraq might use them, both this knowledge and the consequential use of respirators and protective suits were thought to be stressful.[12]

The naval contingent was the largest component of the ADF, providing the CDT, helicopter crews and supporting technicians and ships' companies for *Adelaide*, *Darwin*, *Success*, *Brisbane*, *Sydney* and *Westralia*. RAN medical officers commanded the three Task Group Medical Support Elements deployed to USNS *Comfort*, and RAN Health Services personnel supplemented by Army and Air Force made up these medical teams. Other Navy personnel served with USA and UK forces while on exchange, one of whom was awarded a bravery medal after a rescue mission inside Iraq (personal communication ADF personnel).

Army personnel were deployed as missile gunners and linguists with Damask I and II, the Army also deployed with USNS *Comfort*, in Operation Habitat and seven men were with UNSCOM.[6] Army intelligence officers served in the Gulf area over undisclosed dates. Nine Army personnel served with UK forces during Operation Desert Storm and a further nine with the US Army or Marine Corps; they were on exchange with the unit when it was deployed to the Gulf.[6]

The Air Force did not have a direct combat role in the Gulf War but a number of Air Force personnel served there, drawn from many squadrons and units. The primary roles were those of logistic support such as transport for Operation Damask and Operation Ozone (Operation Ozone involved the evacuation of Australian and other Commonwealth persons from the war zone). Flights were made to many parts of the Gulf region including Riyadh, Amman, Muscat and Bahrain.

Some members of the Air Force were based in Riyadh for liaison purposes. Air Force personnel from 33 squadron were based in Cyprus over the period and personnel from 37 squadron were deployed to Cocos (Keeling) islands and then Singapore.[6] Air Force intelligence officers (mainly photographic interpreters) served in Gulf area over undisclosed dates.[7] Twelve members of the Air Force were on exchange with the UK and USA and served with those forces. Air Force personnel also served in Operation Habitat and in the TGMSEs on USNS *Comfort*.[6]

2.2.8.1 Nominal Roll

Following the Gulf War, DVA compiled a Nominal Roll of all Defence Force personnel who served in the operations listed above. The Nominal Roll includes people who were on permanent posting and temporary attachment.

More details on the Nominal Roll are presented in the Cross-Sectional Study Methods and the Recruitment chapters.

Figure 2.2 Gulf War Timelines

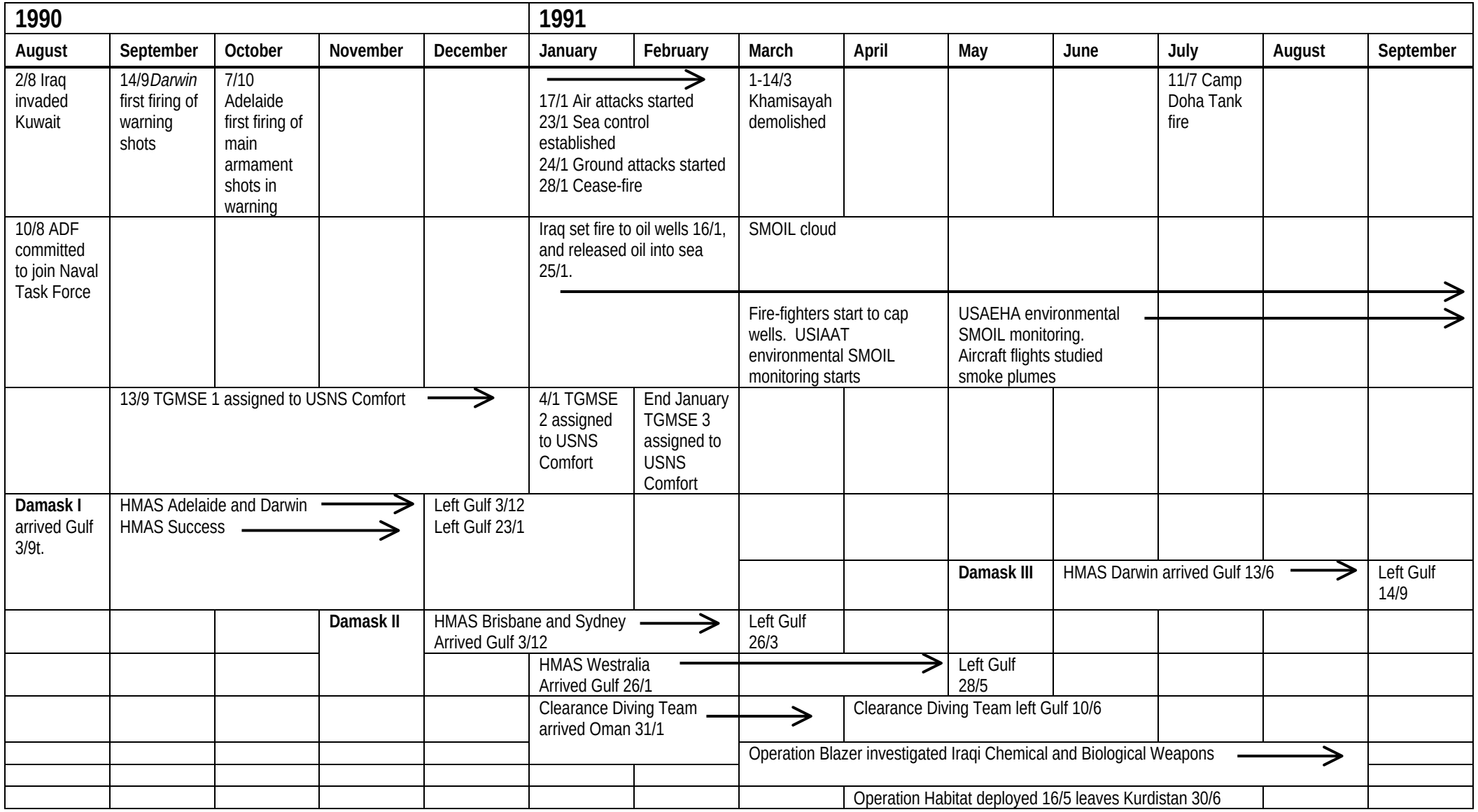


Table 2.1 Key Dates in relation to the Australian Gulf War deployment, after the chronology of events[1-8]

2 Aug 1990	Iraq invades Kuwait
8 Aug	Initial U.S. Air Force fighter planes arrive in Saudi Arabia
10 Aug	ADF committed to Gulf Naval Task Force
mid Aug	***Darwin*** and ***Adelaide*** leave Sydney
22 Aug	***Success, Darwin*** and ***Adelaide*** leave Rockingham, Australia
6 Sept	**Damask I** in Gulf of Oman patrols east of Strait of Hormuz only. Five RAAF Seahawk and Squirrel Helicopters on board ***Success*** arrives in region
13 Sept	**TGMSE 1** RAN Task Group Medical Support Element joined **USNS *Comfort***
14 Sept	***Darwin*** fires 100 rounds of warning shots across a ship's bows
24-26 Sept	***Darwin*** rest and recreation (R&R) Muscat
24-27 Sept	***Adelaide*** R&R Muscat
8 Oct	***Adelaide*** fires two .76mm shots using main armament
21-22 Oct	***Adelaide*** R&R Muscat
21-24 Oct	***Darwin*** R&R Muscat
27-30 Oct	***Adelaide*** R&R Muscat
8-12 Nov	***Darwin*** R&R Muscat
12-16 Nov	***Adelaide*** R&R Muscat
20 Nov	Damask II deployed: ***Brisbane*** and ***Sydney*** leave Western Australia with RAN helicopters on board
29 Nov	UN Security Council authorises use of "all means necessary" to eject Iraq from Kuwait
28-1 Dec	***Darwin*** R&R Muscat
28-1 Dec	***Adelaide*** R&R Muscat
3 Dec	***Darwin*** and ***Adelaide*** leave area of operations to return to Australia
4 Dec	***Brisbane*** and ***Sydney*** arrive Gulf of Oman
6-10 Dec	***Brisbane*** R&R Muscat
14 Dec	***Darwin*** and ***Adelaide*** arrive Darwin Australia
16 Dec	***Brisbane*** and ***Sydney*** go through Strait of Hormuz to central Gulf and Bahrain
21-27 Dec	***Brisbane*** R&R Bahrain
23 Dec	***Sydney*** leaves Bahrain for Gulf
24-28 Dec	***Success*** R&R Seychelles
26 Dec	***Sydney*** was in charge of the interception of the Khaldoon. Searches another ship
31 Dec	**TGMSE 2** RAN Task Group Medical Support Element embark **USNS *Comfort***
30 Dec- 6 Jan 1991	***Sydney*** goes to Dubai (UAE) for new year R&R.
4 Jan	**TGMSE 1** RAN Task Group Medical Support Element disembark **USNS *Comfort*** at Dubai
8-11 Jan	***Brisbane*** R&R Dubai (UAE)

11 Jan	***Sydney*** enters Gulf on surveillance and patrol, escorts ***Success*** to N. Gulf replenishing duties
13 Jan	**TGMSE 3** RAN Task Group Medical Support Element embark **USNS *Comfort***
12 Jan	USA Congress authorises use of force
15 Jan	UN deadline for Iraqi withdrawal. ***Westralia*** leaves Australia
17 Jan	Allied attack begins with Tomahawk strike at 2:38 am. Red air and surface warnings issued.
19 Jan	***Sydney*** escorts US Ship to Bahrain and 2 days later returns with another US ship
23 Jan	Allies report Sea Control established. ***Success*** leaves Gulf for Australia
24 Jan	Red air warning on HMAS Sydney, air attacks to the north and a flash to the south east
25 Jan	Iraqis release oil into Gulf and start setting fire to oil wells; SMOIL spreads
26 Jan	***Westralia*** arrives in the Gulf, going to Muscat then to Bahrain
27 Jan	***Sydney*** escorts US ship back to Bahrain
31 Jan	**Clearance Diving Team** arrives in Muscat from Australia. Sent on to Bahrain on ***Westralia***
Early Feb	***Brisbane*** close to Iranian coast then later in northern Gulf area south of Dorra oil fields near Kubbar Island. ***Sydney*** close to Iraqi coast
5 Feb	***Westralia*** goes into Gulf to replenish ***Sydney*** and ***Brisbane***
9 Feb	Satellite pictures show SMOIL cloud
16 Feb	VII Corps moves into final attack positions
19 Feb	***Sydney*** under likely silkworm missile attack, Red air warning. Nearby US ship hits mine
23-28 Feb	***Westralia*** in Dubai to replenish ***Sydney***, remains in central Gulf on replenishment duties after cease-fire
24 Feb	Ground attack begins
26 Feb	Iraqis flee Kuwait City, ***Success*** arrives in Australia
28 Feb	Cease-fire takes effect at 8 am.
27-2 March	***Brisbane*** R&R Dubai
March	**Operation Blazer** sends 5 men to support UNSCOM. ***Sydney*** in Gulf of Oman on escort duty for US battleships leaving Gulf. Escort duties for replenishment ships until 14 Mar goes close to Kuwait city. ***Brisbane*** escorts US ships in northern Gulf; sights sea mines. Chemical weapons destroyed at Khamisiyah.
2 March	**Clearance Diving Team** goes to Kuwait and starts mine clearance work in thick oil slick
7 March	***Sydney*** in severe dust storm
15 March	**TGMSE 2** and **TGMSE 3** disembark **USNS *Comfort*** at Bahrain
15-22 March	***Brisbane*** R&R Bahrain
15-23 March	***Westralia*** in port at Dubai
23 March	***Westralia*** meets ***Sydney*** and ***Brisbane*** in Gulf of Oman, replenishes then returns to Gulf
26 March	***Brisbane*** and ***Sydney*** leave Gulf
8-11 April	***Westralia*** in port at Abu Dhabi
10 April	***Darwin*** leaves Darwin, Australia for second deployment
12 April	Formal cease fire announced
14 April	***Brisbane*** arrives Darwin, Australia
18-22 April	***Westralia*** in port at Muscat

19 April	**Clearance Diving Team** complete task
2-6 May	***Westralia*** in port at Dubai
10 May	**Clearance Diving Team** returned to Australia
14-16 May	***Westralia*** in port at Bahrain
16 May	**Operation Habitat** deployed to Kurdistan in northern Iraq
19-20 May	***Westralia*** in port at Al Jubayul
21-24 May	***Westralia*** in port at Dubai
28 May	***Westralia*** leaves Gulf from Dubai
31 May	**Damask III, *Darwin*** (2nd deployment) leaves SE Asia for Gulf
9 June	***Westralia*** arrives Fremantle, Australia
13 June	***Darwin*** arrives in Gulf. Carries out surveillance, minesweeping protection, USS aircraft carrier and merchant ship escort through mine cleared areas. Ports of call include Muscat & Wudam (Oman), Dubai & Abu Dhabi (UAE), Doha (Qatar), Ash Shliywaikh (Kuwait) and Bahrain
30 June	**Operation Habitat** completed
11 July	Fire in Tank compound, Doha (Qatar)
4 Sept	***Darwin*** leaves Gulf
21 Sept	***Darwin*** arrives in Darwin, Australia

3. Review of literature on exposures during the Gulf War

3.1 Introduction

This chapter reviews the available data relating to overseas forces in the Gulf and attempts to assess which are of most relevance to Australian forces. This review has been assisted by considerations of relevant aspects of Australia's involvement in the Gulf War covered in the previous chapter and also examination of the logs of Australian ships sent to the Gulf.

The chapter focuses on the exposures and experiences of most relevance to the Australian Gulf War deployment. There were many potentially health-threatening exposures during the Gulf War that have been investigated in previous studies. They are presented in Table 3.1. These studies have been carried out on forces from overseas countries. However, the exposures and experiences that are described are also likely to be of importance to Australian Gulf War veterans, but the extent of exposure is likely to be different from that of overseas veterans. There is little published information on these exposures for Australian Gulf War veterans. However, extrapolations from exposure data related to overseas forces to Australian Gulf War veterans can be made in order to assist in clarifying which Gulf War exposures and experiences an Australian study should focus on, in consideration of possible links between such exposures and health outcomes.

Health threatening exposures during the Gulf War include:

- *War-related exposures;* eg smoke from burning oil wells, psychological stressors
- *Job-specific exposures*; eg paint, exhaust fumes
- *Preventive health measures*; eg immunisations, antimalarials
- *Hazards from the environment*; eg heat or cold, sand

The specific components of these groupings are outlined in Table 3.1, along with the references for literature about these exposures. Some exposures were unique to the Gulf War deployment, or very uncommon outside that deployment. Examples of these exposures include pyridostigmine bromide (PB), concern about possible exposure to biological and/or chemical warfare agents, and particular immunisations such as for plague or anthrax. In the subsequent sections of this chapter, we examine each of the exposures in Table 3.1 and try to assess their relevance to ADF personnel deployed to the Gulf.

Table 3.1. Potential Gulf War exposures and the studies which have investigated them

Exposure	Study Reference
War-related exposures	
Psychological stressors	[13-27]
Smoke and oil cloud (SMOIL)	[16, 17, 19-23, 26-42]
Chemical warfare agents including nerve gas and mustard gas	[16, 17, 20-22, 27, 29, 31-35, 38-40, 42-47]
Hearing chemical alarms	[17, 20-22, 39, 41, 43]
Wearing chemical protective clothing/respirators	[17, 20-22]
Depleted uranium including being inside destroyed Iraqi tanks	[17, 20, 22, 23, 27, 31-34, 39, 40, 44-46, 48-51]
Smoke from burned excrement/waste	[20-23, 27, 32, 36, 38, 39]
Exhaust fumes including use of tent heaters	[21-23, 26, 27, 29, 31-33, 38, 41]
Job-specific exposures	
Petroleum products including fuels, paints and solvents inhalation, skin and on ground	[16, 17, 19-22, 26-29, 31-36, 39-41, 44]
Chemical resistant agent (CARC) paint (contains isocyanates)	[17, 20, 27, 31, 33, 44, 46, 52]
Preventive health measures	
Immunisations and other prophylactic medications	[12, 15, 17, 21, 25, 26, 28, 41, 53-69]
Pyridostigmine bromide (PB or NAPS tablets)	[16, 17, 19-21, 23, 26-29, 31, 33-35, 38-40, 44, 45]
Pesticide use or exposure (insecticides and rodenticide) including flea collars and use of pesticide treated clothing and bedding	[16, 17, 20-23, 26-29, 31-35, 38, 40, 44, 45, 61, 70]
Insect repellent, particularly DEET-based repellents	[17, 19-22, 27-29, 31-33, 35, 38, 40, 41, 45]
Use of sunscreen	[26]
Hazards from the environment	
Desert sand	[19, 26, 27, 32, 35, 36, 40, 44, 71, 72]
Infectious agents	[16, 17, 19, 31, 34, 40, 44, 69, 73]
Local or non-military issue foods	[20-22, 26, 27, 32, 33, 35, 38, 39]
Contaminated food	[20, 22, 26, 27, 32, 33, 35, 46]
Non-US or contaminated water (bathed, tooth brushed or drank)	[20, 22, 23, 26, 27, 32, 33, 35, 36, 39, 46, 71]
Mammal, reptile, scorpion or insect bites	[17, 27, 32, 35, 36, 69]
Extremes of heat and cold	[17, 19, 22, 27, 35, 36, 69]

3.2 Smoke from oil well fires (SMOIL)

3.2.1 Background

In January and February 1991 the Iraqis deliberately set fire to 788 of 943 Kuwaiti oil wells and damaged a further 175.[74] Smoke from the burning oil wells was visible on satellite pictures from 9th February.[75] Close to the fires, oil drops fell from the smoke, coating the desert with a tar-like covering. Pools of oil formed from damaged, but not burning, well heads and these released vapours into the air; some of these caught fire.[76]

The oil fires released 3,400 metric tons of soot into the environment over a ten month period to November 1991 and burnt more than 4 million barrels of oil a day.[36] Kuwaiti crude oil has a relatively high sulphur content, 2.25% by weight, and estimates suggest that the total amount of sulphur emitted was approximately two thirds that of UK annual emissions from coal-fired power stations.[77] Other components of crude oil combustion are oxides of carbon and nitrogen, volatile organic compounds and polycyclic aromatic hydrocarbons. The oil also contains trace amounts of various metals including vanadium.[78] Between a quarter and a third of the oil wells gave off white smoke containing sodium and calcium chlorides.[78] Low concentrations of carbon monoxide were measured high in the plumes in May and June, suggesting that combustion was relatively efficient.

The smoke from the oil wells coalesced and was carried over the Gulf by northwesterly winds.[36] The last well was capped on 6th November 1991.[77]

3.2.2 Plume dispersal

The SMOIL was primarily in eastern Kuwait, mostly south of Kuwait City. There was a reduction in the solar radiation recorded on the ground near Jubail, of between 25 and 44 % between February and September 1991 compared to these same months in the previous two years.[74] The smoke obscured 75-80% of the sun's radiation in some parts of the Gulf.[76]

It is thought that the heat generated in the fires, solar heating and the local strong northwest winds and weather conditions elevated the plume to 10,000-12,000 feet, well above ground level[75] without much mixing down to the surface.[79] On most days therefore, although the smoke was visible and perhaps reduced sunlight at ground level, it was not inhaled by the local civilian or military personnel.[75] The plume occasionally went to ground level enveloping some troops.[15] On other days, because of temperature inversions, some US troops reported being soaked at times with unburned oil.[75] Oil spray and drops were deposited on the ground within 50 km of the source.[79]

The plume moved southeasterly down the Gulf, close to the west coast over the months of February to May. The presence of SMOIL was noted in Australian ships' logs between March and July 1991 but usually as a reduction in sunlight, suggesting that the SMOIL clouds were at high level.[2, 4] There was a record of the SMOIL reducing visibility on 2nd July 1991 in the *Darwin*'s ship's log, suggesting that the SMOIL was at a lower level.[2] USNS *Comfort* was anchored off Khafji in northern Saudi Arabia in late February 1991 and was enveloped in SMOIL.[80] Plume frequency distribution maps are available for February to May 1991 based on satellite images (Figure 3.1 to Figure 3.4). They show the areas covered but do not indicate the height of the plume. These plume maps indicate that HMAS *Sydney* and *Brisbane* were within the area covered by the plume during most of March, while HMAS *Westralia* was probably outside the area of the plume for most of its deployment. HMAS *Darwin*, on its second deployment, would have sailed under the plume. HMAS *Success*, *Adelaide* and *Darwin* on its first deployment, would not have had exposure to SMOIL.

Figure 3.1 Oil well fire smoke plume Feb 1991[75]

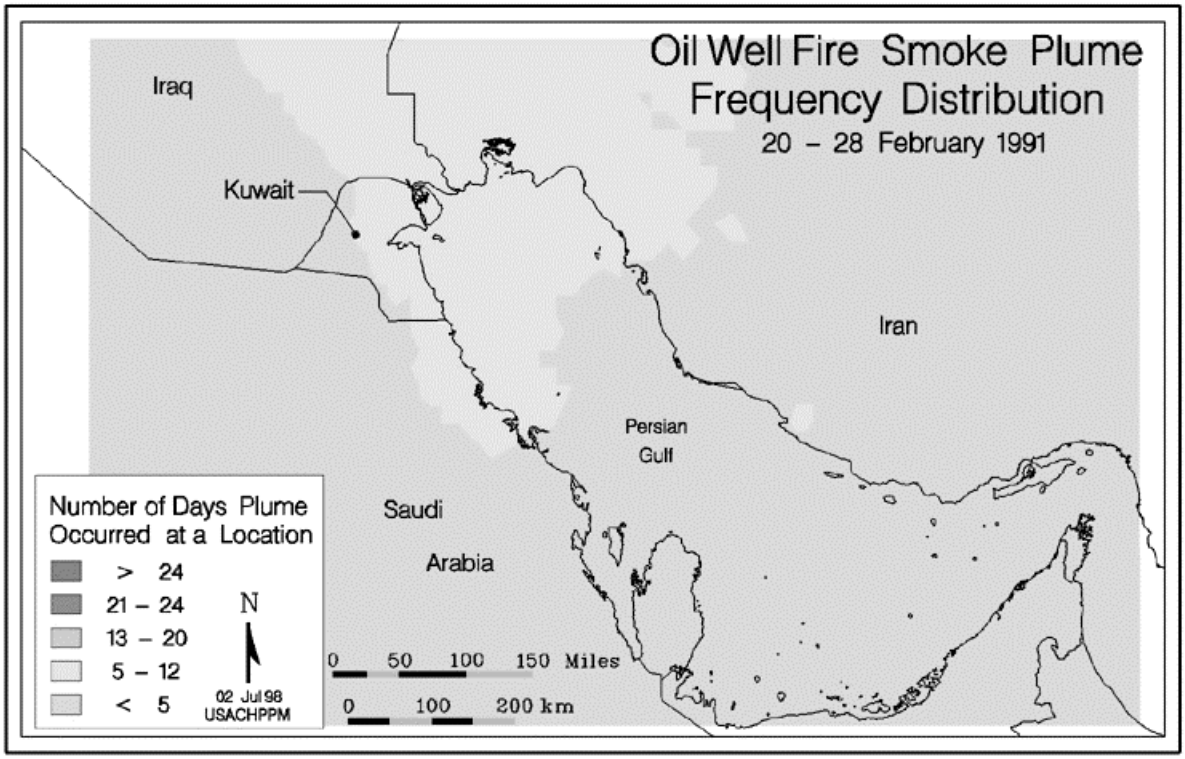


Figure 3.2 Oil well fire smoke plume March 1991[75]

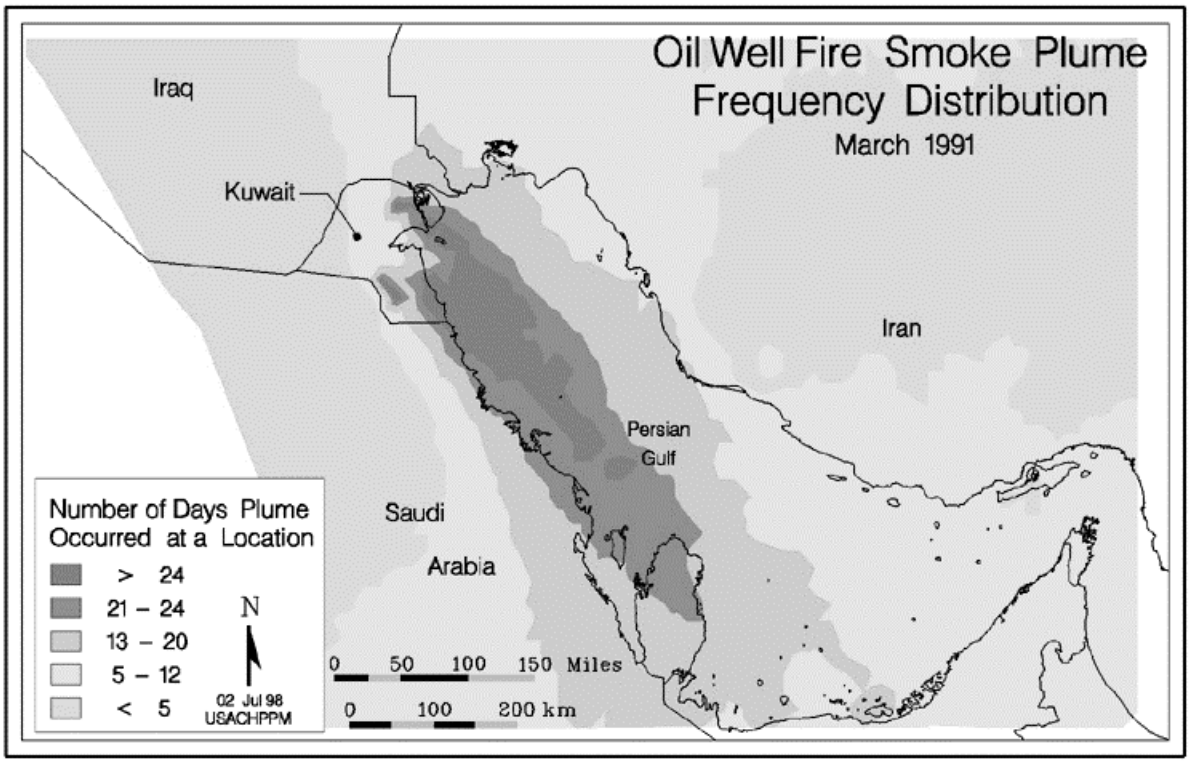


Figure 3.3 Oil well fire smoke plume April 1991[75]

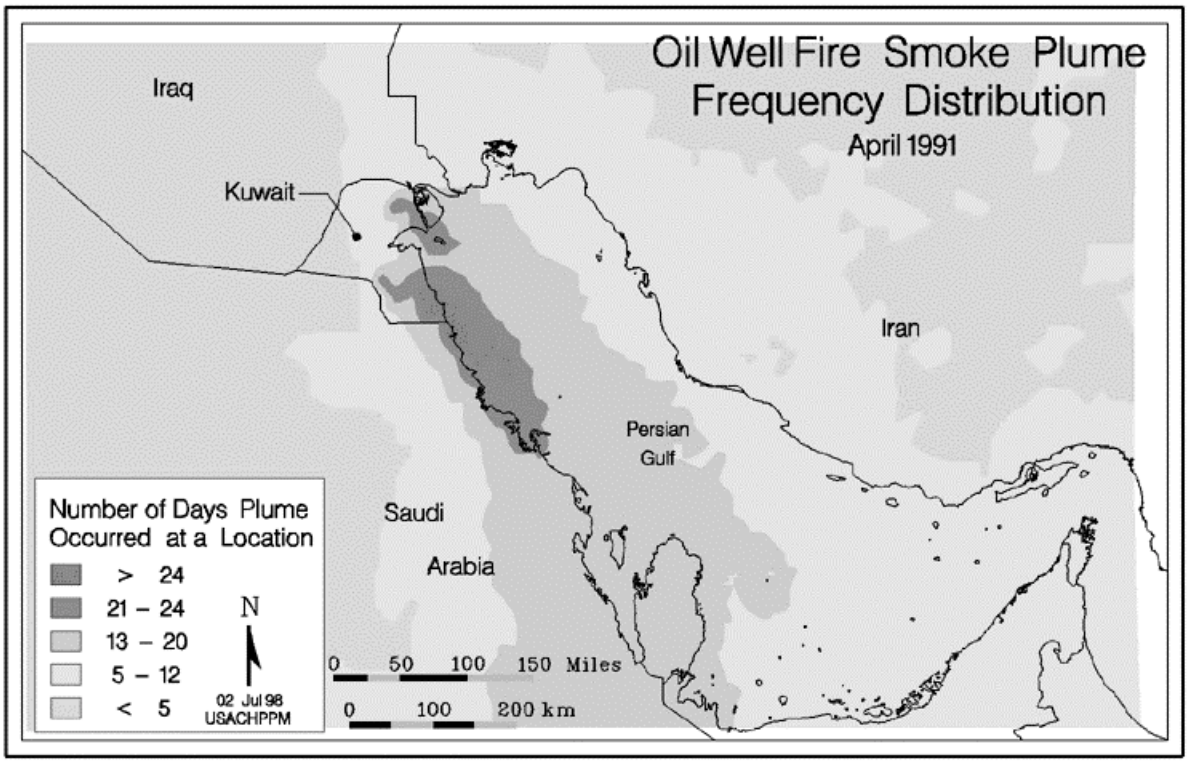
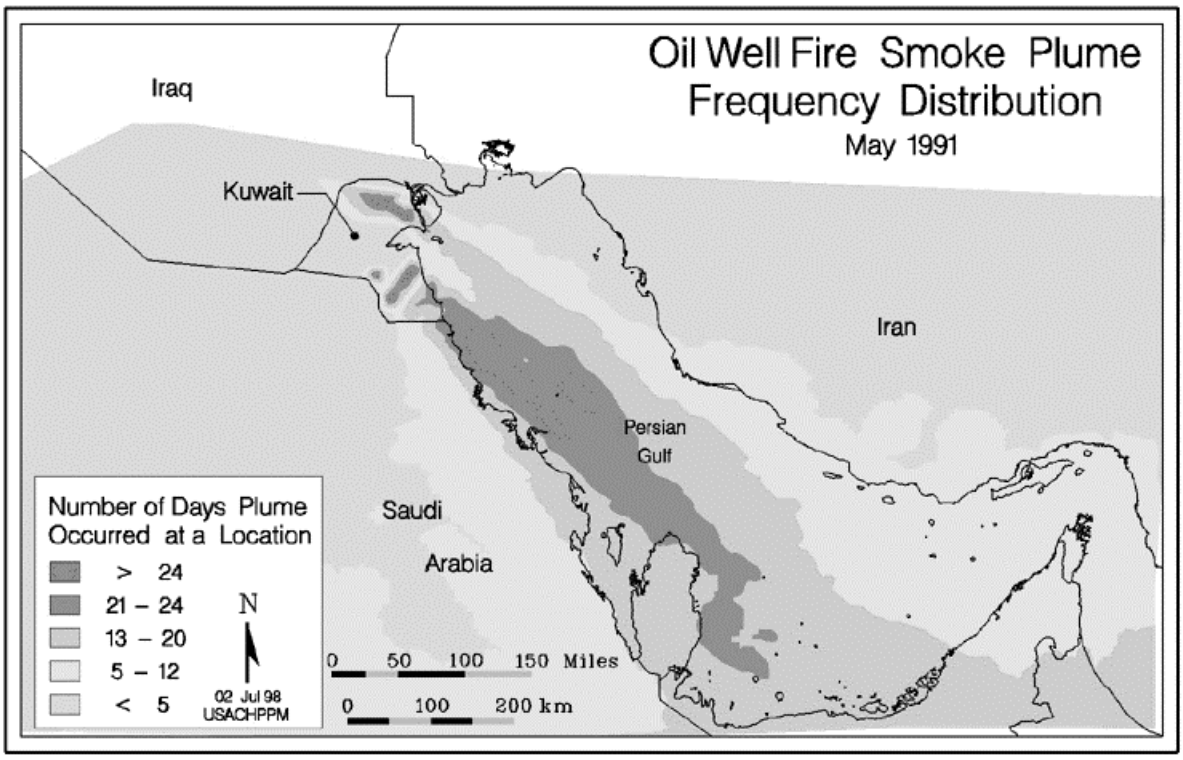


Figure 3.4 Oil well fire smoke plume May 1991[75]



3.2.3 SMOIL exposure measurements

Exposure measurements were undertaken from March 1991 by various international teams which included:

- The US Interagency Air Quality Assessment Team (USIAAT), assembled by the US EPA, began exposure monitoring at 13 ground level locations in Kuwait and Saudi Arabia in March 1991 for the following pollutants: total suspended particulates (TSP), SO2, H_2S, inorganic acids, polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs).
- The US Army Environmental Hygiene Agency (USAEHA) carried out air and soil sampling between May and December 1991, at several sites in Kuwait and Saudi Arabia. They focussed on locations where members of the US DoD were working. 4000 environmental samples were collected and measured for 8 VOCs, including benzene, toluene and xylene (BTX); 24 PAHs including benzo(a)pyrene; acid gases such as sulphuric acid, SO_2, ozone, NO_2 and NO; 19 particulates and metals including TSP and inspirable particulate with an aerodynamic diameter less than 10 microns (PM10).[75]
- The World Meteorological Organization (WMO) was sponsored by the UN to co-ordinate an air quality monitoring programme between March and June 1991, involving scientists from 12 countries including Kuwait. A variety of pollutants were monitored at ground level and in the plume.[75]
- The Research Institute of King Fahd University of Petroleum and Minerals collected data after January 1991 on gaseous pollutants in various ground level locations in Saudi Arabia.

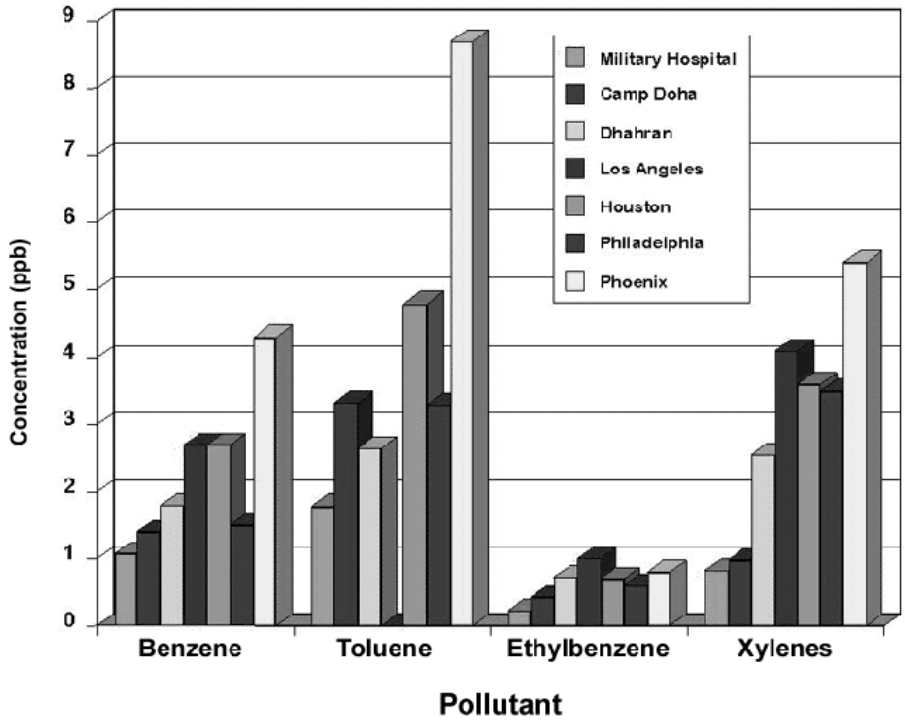
The USIAAT measurement results were compared to USA EPA's National Ambient Air Quality Standards (NAAQS) and Saudi Arabian Meteorology and Environmental Protection Administration (MEPA) NAAQS. Most SO_2 and H_2S measurements were below NAAQS. Levels for inorganic acids, VOCs and PAHs fell below occupational exposure limits.

The USAEHA exposure monitoring results showed that apart from ozone, almost all of the mean and maximum values of the pollutants were several orders of magnitude below relevant occupational exposure limits.[81] Ozone was found in lower concentrations than those recorded in many US cities.[81] The USAEHA BTX monitoring results suggest that exposures are similar to or less than exposures in US cities such as Los Angeles[36, 75] (Figure 3.5). SO_2 and VOC measurements were much the same as samples taken in Kuwait and Saudi Arabia before the war.[75]

WMO measurements showed that almost all the measurements for SO_2, NO_2, ozone, H_2S, and CO were below established standards such as US NAAQS and below the very similar MEPA air quality standards.[75] PAHs measurements were below NIOSH limits but soot exceeded WHO guidelines.[75]

The measurements in Saudi Arabia, taken by King Fahd University for SO_2, NO_2 and CO were below MEPA air quality established standards.[82] Other measurements taken in Saudi Arabia for ozone, H_2S and non-methane organic carbons were within MEPA standards.[83]

Figure 3.5 Median Volatile Organic Concentrations Comparisons Kuwait, Saudi Arabia, US Cities[75]



The highest measurements were made in the plume, high above ground level, with SO_2 detected at 0.68 ppm and a variety of VOCs were detected at between 10-20 ppb. Even where the plume reached ground level, exposures were low compared to US occupational exposure standards.[15] Vanadium in the atmosphere remained low.[77]

Since the Gulf War, the US Army Center for Health Promotion and Preventive Medicine (CHPPM) in collaboration with the National Oceanic and Atmospheric Administration modelled three dimensional exposure to SMOIL over the entire Gulf War theatre of operations.[42] Using geographic information systems data, estimates of daily exposure have been made for each troop unit in the US Army. This has been used to generate individual exposure estimates for each member of the troop units. In a study of regular active duty of Gulf War veterans, 17% were estimated to have had no exposure, 34% had exposure in the lowest category (average daily exposure estimated as 1-260 μgm^{-3} for 1-25 days) and 9% were in the most heavily exposed category (average daily exposure estimated as greater than 260 μgm^{-3} for more than 50 days).[42] Using these modelled data, it would appear that US veterans do not have an increased risk of post-war morbidity associated with exposure to SMOIL.[42]

Blood concentrations of polycyclic aromatic hydrocarbons were measured in a group of 61 Army soldiers deployed in 1991. Blood samples were taken prior to deployment, during deployment, and post-deployment. The results were compared with air and soil measurements of PAHs obtained from areas where the soldiers were working in Kuwait, along with literature values for ambient PAH concentrations in the areas where the troops were stationed prior to and post-deployment. Results indicated that there was no evidence of increased PAH in the blood of soldiers stationed in Kuwait[37] and that long term exposure was probably higher for troops stationed in Germany.[84]

In summary most exposure measurements were below established NAAQS and below occupational exposure limits except for TSP (see section 3.3), PAHs and soot. It should be borne in mind, however, firstly that occupational exposure limits are usually applied to workers with a 40-hour week made up of eight-hour days. This provides periods away from exposure when recovery, if needed, might occur. The exposures described here were intermittent but could have occurred for several days in a row for 24 hours per day. Secondly, it is possible that the measured exposures underestimated the exposures that took place in January and February because 20 of the oil wells had been extinguished before most of the monitoring took place and conditions were probably worse during the winter when the air was stagnant.

3.2.4 SMOIL exposure recall by veterans

Some US veterans appeared to have experienced no problems with the SMOIL. Others, who were close to the oil wells, were "literally drenched" in unburnt oil and/or covered with fall-out (ie, soot, smoke, and other by-products of combustion) from the oil well fires. These exposure incidents, while intense, were generally short in duration lasting from a few hours to several days.[75]

Other US veterans reported exposure to intense smoke and short term symptoms at the time of the exposure, including coughing, black mucous, nasal discharge, eye and throat irritation, and the onset of skin rashes and shortness of breath.[75]

Between 61 and 96% of US veterans reported exposure to SMOIL in several studies.[16, 19-21, 28, 33, 38] 41% of US troops surveyed soon after returning from the Gulf had been within a mile of an oil well fire. 77% of troops spent more than five hours outside per day.[36] Approximately 46% of Danish Gulf War veterans reported exposure to SMOIL.[32]

In summary many Australian veterans, including those whose deployment finished before the air war started, will have had no exposure to SMOIL. Some members of the ADF could have had exposure to SMOIL as evidenced by the ships' logs and comparison of the position of the ships relative to the spread of the plume visualised by the satellite images. A few veterans, mainly those on USNS *Comfort* and the Clearance Diving Team were probably the most highly exposed.

3.3 Particulate matter

Sand in the central and eastern Saudi Arabian Peninsula, including Kuwait, is exceptionally fine.[71] Sand and dust storms occur naturally in this area and are worse during the northern hemisphere summer when the north-easterly Shamal winds occur.[85] The combination of wind and sand, made skin and eye protection necessary during the war.[25]

Elevated levels of airborne particulate matter (ie PM_{10}) were observed at several monitoring sites.[75] Concentrations of suspended particulates (<10µm diameter particles) exceeded MEPA daily average standard (340 μgm^{-3}) at most locations measured between May and October 1991.[83] However the PM_{10} in Kuwait had a high background rate of 600mgm^{-3}. Pre-war monitoring suggested that sand, rather than smoke, was the main constituent. 75% of particulate exposure originated from the sand, a further 23% from the SMOIL and the remaining 2% from several other sources eg engine exhaust.[85]

In one survey 19% of US troops reported that sandstorms were the worst part of the deployment.[36] A peer-reviewed report prepared for the Office of the Special Assistant for Gulf War Illnesses estimated the exposure by US troops to respirable silica and soot and also

dermal exposure to these agents.[72] This report suggested that there were unlikely to be any consequent long-term health effects for US land troops for these exposures.

For most Australian veterans, who spent most of their time at sea, the exposure to soot and silica would be less that that reported for ground troops. There is one record in an Australian ship's log of an exercise being cancelled because of a sandstorm[4] and a second record of sand in the air reducing visibility on 17th July 1991.[2]

3.4 Psychological stressors

The US Presidential Advisory Committee on Gulf War Veterans' Illnesses[15] reports that the US service members encountered many stressors in relation to service in the Gulf War. These included "uncertainty about length of deployment, isolation and separation from family, a polluted environment, poor living conditions with little privacy or social outlets, prolonged work hours…fear of SCUD missile and chemical and biological weapon attacks, anticipation of high casualty rates and torture, frequent (chemical weapon) agent alarms that often required a defensive posture and full chemical gear, and dealings with casualties and dead bodies".

Specific psychological stressors investigated in the international Gulf War literature include fear for personal safety,[18] witnessing combat or civilian casualties,[19, 20] tasks related to mortuary duties,[13, 14] other exposure to dismembered bodies or persons maimed or seriously injured,[21, 22] belief of exposure to chemical warfare agents[17, 21] and coming under small arms fire, other artillery or missile attack.[22]

The first Australian deployment to the Gulf departed within a few days after the invasion of Kuwait by Iraq. This sudden deployment, and subsequent deployments of Navy, Army and Air Force personnel, would have been accompanied by much uncertainty about the eventual progression and outcome of the Gulf War, its length, level of combat and casualties and the use of biological and chemical weaponry by the Iraqis. This is supported by the statement made in January 1991 by the Australian Prime Minister of the time, that "war is full of terrible uncertainty. We cannot foretell what will be demanded of our serving men and women… We hope, above all, that they will return safely home".[86] In personal correspondence, which was later published in The Sydney Morning Herald,[87] one deployed sailor expressed a fear, potentially felt by many other Gulf War veterans at the time, by telling his wife to "be ready for his death".

The patterns of psychological stressors, experienced by Gulf War veterans, may have varied depending on the time of their deployment. Some Australian veterans completed their deployments prior to the commencement of the air warfare in January 1991. Others were still in the Gulf region during this time and during the period of the subsequent ground war and torching of the oil wells. Other veterans arrived in the Gulf region after the actual combat had ceased. Despite the brevity of the air warfare (40 days) and ground warfare (five days) many of the members of the ADF were deployed for several months. Many Navy personnel spent months in the Gulf area patrolling the Strait of Hormuz. As previously described in chapter 2, there were stressful interactions with foreign shipping including the boarding of hostile ships. There were sightings of mine and mine-like objects and possible hostile overflies. The frequent sounding of chemical alarms and the consequent use of respirators and full body suits was, in itself, considered a stressful aspect of duty.[24] The members of the TGMSE's on USNS *Comfort* were called on to participate in the management of injured service casualties including burns victims of the USS Iwo Jima explosion, medical

evacuations and gun shot wounds (Kerry Delaney personal communication). Some Australian personnel were involved in the handling of human remains.

Ground-based members of the ADF such as those on Operation Habitat members presumably experienced similar polluted environmental conditions and cramped living conditions as those reported for other international ground-based forces. This would have included long periods in hot and dry or later cold and damp conditions in crowded, makeshift buildings and tents.[17, 25] In personal communication with the Monash study team, members of Operation Habitat reported coming under sniper attack, living with poor food and water supplies, being exposed to very sick and dying refugees and observing local evidence of the use of chemical warfare.

In personal correspondence and in a variety of presentations to seminars and committees, Australian Gulf War veterans have reported some of the following stressful deployment experiences:

- Constant fear for one's life;
- Constant threat of hitting floating anti-ship mines when aboard ships stationed in the Gulf, or the threat of being struck by Exocet missiles or Silkworm anti-ship missiles;
- Constant threat and fear of chemical or biological weapons attack;
- Exposure to dead and decaying bodies;
- Fear of entrapment below the waterline on ships;
- Inadequate medical training and preparation to deal with sick and dying refugees;
- Uncertainty in relation to the environmental cause for chemical alarms regularly sounding;
- Difficulty breathing, skin burns and rashes as a result exposure to dust and/or oil and/or chemicals in the air.

There is little published documentation of the psychological stressors experienced by Australians during the Gulf War. However, whilst the combat and conditions experienced by Australia's primarily naval contingent are likely to have differed somewhat from the experiences of the larger multi-national ground forces, many of the stressors described by the US Presidential Advisory Committee[15] and in the broader literature, appear to be relevant to the Australian experience.

3.5 Immunisations and other prophylactic medications

The protocol for immunisation of troops from different countries was not uniform. In general, US troops were brought up to date with immunisation for tetanus-diphtheria, polio, MMR, typhoid, yellow fever, influenza and immunoglobulin. In addition, some US troops were given hepatitis B vaccine, meningococcal vaccine, botulinum toxoid vaccine (given to approximately 8000 troops) and/or anthrax vaccine (given to about 150 000 troops). Most US veterans did not require numerous immunisations prior to deployment to the Gulf as they had received full immunisation on first entering the military.[88]

The general protocol for immunisation of UK troops included tetanus-diphtheria, polio, typhoid and yellow fever vaccines (when required), as well as cholera and/or hepatitis B for some veterans. In addition, some troops were immunised against other agents for example anthrax (with pertussis as an adjuvant) and/or plague.[88]

32% of UK veterans had their immunisation records and 40% reported receiving no immunisations.[21] 30% of all UK Gulf War veterans, including 19% of the Royal Navy

veterans received more than 6 inoculations.[28] 26% of UK veterans reported that they had been immunised against plague and 57% reported immunisation against anthrax.[21]

Immunisation procedures for the Australian Defence Force are set out in JSP (AS) 702. The aim of immunisation in the Services is specified as "to protect the health and overall effectiveness of Service personnel and on specified occasions, their families, and to prepare them for service overseas". Initial immunisation is given during basic training, and the currency of immunisation should be maintained with booster doses of some immunisations throughout an individual's military service. Immunisation history is checked prior to a specific deployment, and brought "up to date" as necessary. In addition, immunisations and medications deemed appropriate for that particular deployment, according to a health risk assessment process, are given. Individuals therefore may receive a combination of routine and specific immunisations prior to any deployment.

The Surgeon General, ADF, promulgates any specific immunisation or medical countermeasure requirements for military personnel. For the Gulf War deployment this went out as a message telex and the specific requirements were as follows. All members deploying overseas were to be medically fit for service anywhere in the world and not in need of dental treatment. Confirmation of medical fitness was required. A chest X-ray was not required but personnel were to be tested for HIV prior to departure.

Gulf War personnel were to be immunised as follows:

- ADT
- Sabin (Polio) (oral)
- Hepatitis A (gamma globulin for 3 months)
- Typhoid (oral)
- Cholera (emphasising limited efficacy)
- Measles
- Hepatitis B (recommended only)
- BCG, if Mantoux negative (recommended only)
- Meningococcal (recommended only)

Prophylactic medications included:

- Pre-treatment against nerve exposure: NAPS (nerve agent pre-treatment set) consisting of pyridostigmine bromide 30mg to be taken every eight hours before and for the duration of period of exposure.
- Malaria prophylaxis: doxycycline 50mg daily and chloroquine 300mg base weekly.

Malaria prophylaxis should have been taken by those entering (or about to enter) a malarial area, and this would predominantly apply to a land environment. Antimalarials may have been taken by Navy personnel on shore visits, although they are not usually required in major ports. Malaria prophylaxis may have been taken for a variable period of time.

Other measures included:

- Treatment of nerve agent poisoning: The mainstay was pre-treatment. The recommended medical treatment was diazepam and atropine. Members of the ADF were also issued with self-help, ie auto injection with combopen (which contains toxogonin and atropine) to use in the event that they were subject to chemical warfare.
- Treatment of biological agent exposure: Ciprofloxacin 500mg bd.

It was up to the ship/unit to arrange for each individual being deployed to the Gulf War to be prepared in accordance with these requirements.

The use of prophylactic and other medication may have varied considerably between individuals, ships and units depending on their perceived risk of exposure and self-compliance with medication.

3.6 Pyridostigmine bromide

Pyridostigmine bromide (PB) is a reversible acetylcholinesterase (AChE) inhibitor that was given prophylactically during the Gulf War as a nerve agent pre-treatment set (NAPS).

The USA FDA authorised PB for use by US troops, without informed consent, in December 1990.[55] Its use began on Jan 16 1991.[15] Between 60% and 82% of UK veterans recalled taking PB.[21, 28] 52 to 78% of US veterans recalled taking PB,[16, 19, 33, 35, 38] although only 9% of non-combat troops reported taking it.[35] Ninety-five per cent of US veterans in another study recalled taking PB.[31]

PB has been used in the treatment of myasthenia gravis, an autoimmune disorder of the neuromuscular junction characterised by weakness and fatigability of skeletal muscle[89] for 40 years. It has also been given as a diagnostic test of hypothalamic-pituitary function in normal volunteers and patients.[90]

At cholinergic synapses, acetylcholine (ACh) released from the nerve endings in response to action potentials activates the post junctional receptors and elicits a response. ACh is hydrolysed to inactive products by the enzyme AChE in the synapse, thereby preventing it from inappropriately reactivating the receptors. If the ability of AChE to hydrolyse ACh is interfered with, ACh accumulates in the synapses, and the excess neurotransmitter is responsible for the pharmacological and the toxicological manifestations of AChE inhibition. Although PB and the organophosphates employed as 'nerve gases' inhibit AChE by binding to it, the organophosphate-AChE bond is much stronger than the PB-AChE bond. Protection from 'nerve agents' such as sarin thus results from preinhibition of AChE with a more readily reversible inhibitor.[90] PB is not an antidote like atropine or toxigonin, and has no value when administered after exposure.

ACh is a neurotransmitter for many neural and neuromuscular systems in the body, and organs are influenced by ACh.[90] Adverse reactions which generally occur at high doses are due to the resultant increase in ACh and include muscarinic reactions (nausea, vomiting, diarrhoea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and heavy perspiration) and nicotinic effects (muscle cramps, fasciculations and weakness). Clinical studies suggest that side effects do not last long and have no residual long-term effects.[89, 90] PB has been traditionally thought to be devoid of central nervous system action because of its restricted ability to cross the blood brain barrier.[90] One study, however, has suggested that there are subtle effects of this drug on cognition, reaction time and complex performance of tasks that does not support this established view of central nervous system (CNS) effects.[90]

In addition to acute toxicity, some ChE inhibitors, particularly the organophosphate compounds, produce other neuropathic and myopathic effects that are unrelated to ChE inhibition. These are described as intermediate and delayed neurotoxicity (or organophosphate-induced delayed neuropathy (OPIDN)). Neither the intermediate syndrome nor organophosphate-induced delayed neuropathy has been associated with exposure to PB.[91]

The Institute of Medicine, on reviewing health effects associated with the use of pyridostigmine bromide, concluded that "*there is sufficient evidence of an association between PB and transient acute cholinergic effects in doses normally used in treatment and for diagnostic purposes*", and "*that there is inadequate/insufficient evidence to determine whether an association does or does not exist between PB and long-term adverse health effects*."[25]

In the treatment of myasthenia gravis, the dosage of PB is generally between 60mg three to five times a day, up to 120mg every three hours during day time.[89] Pre-treatment was used by the military to obtain 10-20% inhibition of whole-blood acetylcholinesterase.[25]

For US personnel, PB was self-administered at doses of 30mg orally every 8 hours for one to seven days while under threat of nerve agent attack.[92] For Australian personnel, pre-treatment against nerve agent exposure consisted of 30mg PB to be taken every 8 hours before, and for the duration of, the period of risk of exposure.

PB was to be used prophylactically by members of the ADF if there was considered to be a reasonable possibility of a chemical weapons attack, and taken as long as the threat was credible. NAPS were commenced on order of the Commanding Officer, based on medical advice. On a ship, the ship's captain would give this order, on the advice of the medical officer and intelligence assessments. Variation in usage may have occurred, because NAPS were self-administered.

3.7 Pesticide use

The term pesticide includes insecticides, herbicides, rodenticides, miticides and fungicides.

Organophosphate (OP) insecticides are AchE inhibitors and acute intoxication produces a complex mixture of muscarinic and nicotinic signs which vary depending on the agent and dose.[93] Acute severe exposure can result in convulsions and death. Fewer than ten US veterans are thought to have sought medical treatment for pesticide exposure.[94] Some OPs induce organophosphorous ester-induced delayed polyneuropathy (OPIDP). This effect is delayed and occurs 10-14 days after exposure, usually after an acute cholinergic crisis.[95] There is some epidemiological and animal evidence of impaired neurobehavioural performance after chronic low level exposure to some OPs.[93] There may be some evidence from the literature that there can be long-term effects following asymptomatic exposure[94] but this evidence is disputed even for possibly hyper susceptible individuals.[96]

Carbamate insecticides act as AchE inhibitors in a similar way to OPs but the effects are rapidly reversible and enzyme inhibition is relatively brief.[97] Permethrin is unlikely to have systemic toxicity in humans, except perhaps the occasional skin irritation or allergic reaction.[97]

There were a number of cases where pesticides were misused by US troops, usually because personnel did not follow the instruction on the product label, eg they failed to use appropriate protective equipment.[94] American studies reported the use of "pet flea or tick collars" by 3% of veterans.[31]

Lindane was used by US military police to delouse prisoners of war (the UK used malathion). It is unlikely that members of the ADF were exposed to lindane.[94]

20-38% of UK veterans reported using pesticide treated clothing or bedding[21, 28] although none of these were in the Navy. 19% of Danish veterans reported exposure to insecticides.[32]

Between 27 and 63% of US veterans reported pesticide exposure or smelling pesticides.[16, 38, 41] A study of Seebees reported pesticide exposure was only 4% however.[26] In a UK study, only 7% of veterans reported handling pesticides, and none of these were in the Navy.[28]

In the Australian Navy, during the Gulf War period, pesticides were used by specifically trained environmental health personnel. Baygon powder and a residual spray (carbamate and permethrin-based pesticides) were used on ships just before embarkation, then as needed. An area would be identified and the ventilation blocked off and the area fumigated. There might have been bystander exposure for personnel in the area. There is no reason to think that the pesticide exposure would have been different on this deployment to that on any other deployment. This has been stated explicitly for the US Navy.[94] There are no available written records for the Gulf War period on pesticide use by the ADF.

Only specially trained members of the Australian Army use insecticides. Insecticides used by the Army include an organochlorine (Dieldrin), organophosphates, (Malathion, Diazinon, Temephos) and carbamates (Baygon, Bendicarb). Clothing and tents were dipped in permethrin (trade name Perigen) and dried prior to use (Lieutenant Commander Chris Maron and M. Dell'Orco, personal communications). The soldiers themselves would have known that they wore treated uniforms but not necessarily have known what pesticide they had been treated with. There is some experimental evidence that pesticides from treated fabric can enter the body.[98]

Pesticides were not used by the Air Force during the Gulf War deployment (Air Commodore Stan Clark, personal communication) nor by most of those troops involved in Operation Habitat (Col. David Ross, personal communication). There was a preventive health section attached to Operation Habitat, which fumigated at the base camp including inside tents and in some Kurdish areas (Col. David Ross, personal communication). The extent of exposure is unknown for Army personnel deployed with UK and USA troops.

3.7.1 Insect repellent use

N,N-diethyl toluamide (DEET) is a pesticide commonly used as an insect repellent. DEET has been marketed over the counter since 1956 and has been widely used. DEET has low transdermal toxicity[99] and is not thought to be a carcinogen or mutagen.[94] The few cases of major DEET morbidity have been associated with its ingestion or with dermal exposure to large amounts.[99]

DEET is normally available in formulations with less than 31% active ingredient.[31] However, one of the formulations available to the Army (MGK 1941) lists the active ingredients as 76% DEET (data sheet supplied by M. Waixell).

Self-reported exposure to repellents varied between studies. Between 27 and 69% of veterans have reported use of personal pesticides.[19-21, 28, 38, 94]

A miticide repellent and varieties of DEET-based insect repellents may have been issued to members of the Australian Army. DEET-based insect repellents would probably have been issued to any ADF personnel going on shore in the Gulf, but were probably not required or used while at sea (Lieutenant Commander Chris Maron, personal communication).

3.8 Biological and chemical weapons

Between 1985 and 1991, Iraq is thought to have developed chemical weapons, including sarin and mustard gas, and biological weapons including anthrax, botulinum toxin and aflatoxin.[100]

It is considered unlikely that Iraq used biological weapons in the Gulf War.[17, 88] Mycotoxins may have been used by Iraq in the Iraq-Iran war.[101] The use of mycoplasma against allied forces in the Gulf War has been postulated[102, 103] but a study of the frequency of infection suggests that this is unlikely.[104]

The deliberate use of chemical weapons by Iraq in the Gulf War has not been confirmed, and is thought to be most unlikely.[17, 73] However, chemical weapons were probably used by Iraq against the Kurds in northern Iraq[25, 58] and in the Iran-Iraq War.[101] The volatility and reactivity of chemical weapons make it unlikely that residues from the previous uses would have affected ADF personnel later deployed to the Gulf, even those on Operation Habitat. There were suggestions that oil well heads were poisoned with chemical or biological warfare agents, which were then spread by the SMOIL plume, however this is also considered unlikely.[75]

Sarin is an odourless, volatile liquid, toxic by inhalation or skin contact. It is an organophosphate which works by blocking the action of cholinesterase so that acetyl choline, a neurotransmitter, is not broken down.[99] High acute exposures cause neurological effects including convulsions, coma and death. Cyclosarin is a similar but more persistent form of sarin.

Data on the health effects of sarin from animal toxicology and human studies, tests on volunteers, exposed industrial workers and victims of terrorist attacks are generally short-term exposures and are limited by a lack of exposure measurements. The longer-term effects of sarin exposure are less well documented.

Mustard gas is in fact droplets of liquid rather than a true gas. It causes burning of the eyes, eyelid swelling, coughing, bronchitis and long-term respiratory system damage.[105] On the skin, mustard gas burns appear at least several hours after poisoning. In mild cases the delay can be 3-4 days. Many tiny blisters occur which may coalesce and this is followed by desquamation producing large raw areas on the skin. Severe cases show bone marrow toxicity and epidemiological studies of manufacturing workers show an increase in cancers of the respiratory tract.[105, 106]

Mustard gas was used by the Iraqis against the Iranians in 1984/5 and against the Kurds in 1998.[105] Between 2 and 7% of USA troops considered that they had been exposed to mustard gas.[20, 33] One US soldier had confirmed mustard gas exposure.[15, 45]

Apart from the risk from direct use of chemical weapons by the Iraqis, there were some incidents of accidental release of these agents. Khamisiyah was a large Iraqi weapons storage complex containing more than 100 bunkers about 120 km west of Al Basrah in the south of Iraq, close to the Kuwaiti border.[40] US troops systematically destroyed ammunition in the bunkers over the first two weeks of March 1991.[25] UNSCOM inspected Khamisiyah in October 1991 and found evidence of rockets loaded with sarin and cyclosarin. Mustard gas shells were also found in the area. It is now suspected that US troops in the area may have been exposed to chemical weapons during the demolition of weapons in two areas known as the “pit” and in bunker 73.

Subsequent modelling by the Central Intelligence Agency and USA Department of Defense (DoD) estimated the extent of exposure to sarin among the US military.[15] They concluded that the likely movement of vapour was from east to north east away from nearby US troops when bunker 73 was demolished. The chemical agent in the plume was estimated as "at least 0.01296 milligrams per minute per cubic meter" but the exposure was unlikely to have been sufficient to cause ill-health.[45] There is more uncertainty over the demolition of the weapons in the pit.

Two other munition storage sites were damaged during air attacks: Muhammadiyat where sarin-cyclosarin and mustard gas were stored and Al Muthanna where sarin-cyclosarin was stored.[15] Atmospheric modelling by the CIA and DoD estimated that the nearest US troops were 400 km away, outside the range of contamination.

The areas that were estimated to be possibly contaminated with chemical weapon fallout following the destruction of stored chemical weapons (based on CIA modelling) did not reach the Gulf waters and consequently make it unlikely that there was any exposure for Australian ships' personnel. However, ADF inspectors with UNSCOM team could have been exposed to chemical weapons during the course of their investigations. More chemical weapons were destroyed in March 1992 as a result of the UNSCOM investigations.

Many US ground troops considered themselves to have been subjected to chemical warfare in the form of nerve gas or mustard gas.[43] Combat troops were more likely to believe that they had been exposed to chemical warfare agents than non-combat troops (63% vs 34%).[35] The proportions of US Gulf War veterans reporting exposure to chemical warfare agents varied in different studies, from 2 to 63%. However those with and without symptoms reported similar exposure prevalence.[16, 20, 33, 38]

At the time of the Khamisiyah demolition there were no medical reports by US Army Medical Corps of signs or acute symptoms suggesting exposure.[15] A study of the hospitalisation of US troops possibly exposed to the fallout from chemical munitions destruction showed no increase in postwar hospitalisation.[107] In a survey mailed to 20,000 troops in 1997, 99% of respondents reported no acute cholinergic effects.[25] A telephone survey carried out in 1999 showed that troops who had witnessed or participated in the demolition, reported more historical or extant symptoms consistent with low level exposure to sarin than troops who did not witness or participate in the destruction.[108] Troops reported to be within 50 km of the Khamisiyah site do not appear to have suffered any long-term health effects consistent with exposure to chemical warfare agents.[47] The seven year mortality follow-up experience of these possibly exposed troops was not significantly different to that of unexposed troops.[109]

The majority of US and UK veterans recalled wearing chemical protective clothing (other than in training) or had heard chemical alarms. However only 9-15 % of these personnel believed that they had been exposed to nerve gas.[20, 21] Nearly 40% of US veterans recalled being on formal alert for chemical attack more than 11 times.[41] UK veterans were more likely to report exposure if they were ill (RR 1.9; 95% CI 0.32-11.8).[29] Only 0.2 % of asymptomatic Danish veterans self reported exposure to nerve gas but 1.4% of those with one symptom of ill-health reported exposure. The difference was not statistically significant.[32]

Haley and Kurt[31] reported symptoms in veterans "who reported having experienced a likely chemical weapons attack". They found an increase of symptoms among those veterans who had been located in the extreme northeastern area of Saudi Arabia on January 20th 1991. According to Haley and Kurt, at this time US planes were bombing Iraqi chemical weapons

storage sites and Iraqi field commanders were authorised to use chemical weapons.[31] In addition, Czechoslovakian experts employed by the Saudi Arabian government detected low level sarin and mustard gas in the area, using wet chemical (ie specific) methods.[15]

US veterans were taught to consider that the presence of dead animals was suggestive of chemical warfare. Since desert nomads are reported to leave dead animals piled in heaps rather than burying them, troops may have mistaken these for evidence of the use of chemical warfare agents.[17] Veterans' belief, that they had been exposed to chemical/biological warfare agents, may have resulted from hearing chemical alarms which was common in many US units.[43] Some of these alarms may have been the result of malfunctions or cross sensitivity/lack of specificity in the reaction of the alarms.

The US Army used two types of electronic detectors, the M8A1 and the M256A. The M8A1 is an automatic ionisation detector designed to detect the presence of nerve agent vapours or inhalable aerosols. It automatically signals the presence of the nerve agent in the air with both an audible and a visible warning. This reaction is non-specific however and the detectors also react to low batteries, high temperatures, sand, smoke, paint fumes, vehicle exhaust, fuel vapours, insecticides and other materials. A more specific enzyme based detector, the M256A1 kit is used after a chemical attack to determine if it is safe to unmask.[110]

US troops also used a paper tape monitor.[111] This monitor can distinguish between different types of chemical warfare agents. On the basis of spot diameter and density on the detection paper, it is possible to obtain an estimation of the original size of the droplets and the degree of contamination. A disadvantage of the paper tape monitor is that many other substances can also dissolve the pigments, eg oil or fuel, although drops of water give no reaction.[110]

The ADF were supplied with colour change electronic detectors and paper tape monitors to detect the presence of chemical weapons. The electronic detectors were probably the same as, or similar to, those supplied to the USA and UK (Commander Ted Walsh (ADF), personal communication).

If the electronic alarms activated, ADF troops in the vicinity were required to use personal protective equipment. Trained personnel in charge of monitoring would then carry out more specific enzyme-based analyses or paper tape analyses to confirm or rule out the presence of chemical warfare agents. Any confirmation was to be documented and passed up the chain of command. Malfunctions/false alarms would give negative results on the enzyme-based assay and would be much less likely to be documented, particularly if repeated and if they occurred during the heat of battle. Australian ships' logs recorded several chemical alarm activations, some were exercises and the remainder were found to be false alarms.[2]

Respiratory protective equipment (respirators) can be used for protection against a variety of inhaled agents, and such equipment was used at times during the Gulf War. Various respiratory and total body protective devices were supplied to Australian troops. Respirator efficiency is dependent on good compliance and fit. Wearing a respirator is stressful for individuals and reduces maximal exercise capability, which impedes compliance. Stressful effects include cardiovascular and pulmonary effects, increased musculoskeletal burden due to the weight of the respirator, the decreased mobility or agility associated with its use, thermal effects because of increased heat loading and reduced ability to cool the body by the evaporation of sweat, especially when respirator use is combined with impermeable clothing. Some users also experience psychological effects akin to claustrophobia. The use of respirators reduces the ability to communicate including; interference with speech, hearing,

effects on vision due to fogging or inability to use contact lenses (particularly hard lenses).[112, 113]

3.9 Interactions between pesticides, PB and chemical warfare agents

There has been concern that exposure to several types of chemical agents which were present in the Gulf War may have an interactive effect.

Animal evidence suggests that there may be interactions or synergistic effects between PB, OPs, DEET and chemical warfare agents but the effects are difficult to extrapolate to humans because of the high doses used in animal studies.[15, 94, 114] It has been suggested that exposure to PB reduces the protective function of pseudocholinesterases and other esterases by hampering the protective function of these enzymes.[115] The extent of this interaction may vary as a result of genetic polymorphisms in humans, in particular for the 4% of individuals who have low scavenger esterase levels.[116-121]

Animal studies suggest that PB, DEET and permethrin, alone or in combination, lead to neurobehavioural deficits and changes to AchE and acetylcholine receptors[122] and that co-administration of these agents produces greater toxicity than does a single exposure.[123-125] A possible mechanism for synergy is that co-administration decreases the blood brain barrier and possibly increases nerve and/or serum concentration of these agents.[122, 123, 126-129] However, animal studies suggest that DEET does not enhance the percutaneous absorption of permethrin or carbaryl (a carbamate pesticide).[130]

Animal studies suggest that the effects of PB potentiate by simultaneous exposure to caffeine and adrenergic agents such as ephedrine.[131] Thus the perception of being exposed to nerve gas may cause an adrenergic load which may potentiate the effect of PB.[132]

There is little clinical human data to show whether these interactions occur in humans. It is also important to note that the levels of exposure in these animal studies are considerably higher than expected in human exposure.

3.10 Depleted uranium

Naturally occurring uranium contains primarily 99.28% of ^{238}Uranium (U) and 0.72% of ^{235}U isotopes.[133] Depleted uranium (DU) is a by-product of the uranium enrichment process, and is composed of three isotopes; ^{238}U (99.75%), ^{235}U (0.25%) and ^{234}U (0.0005%). The chemical and physical properties of natural uranium and DU are essentially identical; however, their radiological properties differ because DU is roughly 60% as radioactive as natural uranium.[134] ^{238}U is primarily an alpha particle emitter with a half-life of 4.5×10^9 years, therefore only internal exposure is significant; clothes will sufficiently protect skin.[25] The decay products emit beta particles and weak gamma rays but because of the long half-life of uranium, only small amounts of these daughter products are present.[135]

DU may present a health risk through its low-level radiological properties or through its chemical toxicity as a heavy metal.[136] Radiotoxicity can result from inhalation of insoluble uranium particles.[136]

A health risk may occur if DU enters the body as shrapnel is inhaled or is swallowed. The amount retained in the body depends on the solubility of the compounds and for inhaled particles, the particle size. Less soluble uranium compounds, from respiratory exposures, tend to accumulate in the lungs and lymph nodes, and, especially if the uranium is enriched

with ^{235}U, such accumulation may cause lung cancer. There is some animal evidence that depleted uranium is mutagenic and genotoxic.[137]

Only 20% of uranium from food is absorbed, with most excreted by the kidney in urine within 24-48 hours. The 10% of DU in the blood that is not excreted is retained by the body and can be deposited in bones, lungs, liver, kidney, fat and muscle.[135] Acute renal failure or necrosis may result from acute intoxication with soluble uranium compounds.[133, 138]

There has been concern that there are trace levels of plutonium and other contaminants that indicate the presence of recycled nuclear fuel in DU. These contaminants are in the part per billion range according to US Department of Energy and US Army testing.[139]

Depleted Uranium is used in enhanced armour protection and in armour piercing munitions such as anti-tank weapons and close in weapons systems (CIWS), because it is dense and self sharpens as the round penetrates the target's armour. The DU fragments on impact, generating large fragments, which can cause shrapnel wounds, and also very fine particles which are small enough to be inhaled into the lungs.[135] The Gulf War was the first war where DU munitions were used, and declassified US documents state that the American military used 944,000 rounds of DU bullets in Iraq and Kuwait.[140]

Australian Defence force personnel could have been exposed to DU in the following circumstances:

- If the CIWS systems on the Australian ships deployed to the Gulf fired American-issued rather then Australian rounds, resulting in possible direct radiation or dust exposure. This exposure is considered to be unlikely, firstly because the Australian government made a policy decision not to use DU weapons (Captain Cawley, ADF personal communication). This is confirmed in the US military web site that states "in 1990, the US had a near monopoly on the use of DU", and, "the only other country known to have fired DU munitions in the Gulf War is the United Kingdom".[135] Secondly, as far as known, apart from test firings, the US Navy deployed their DU CIWS system only once during the Gulf War and this was the only use of DU munitions by any of the coalition naval forces.[135]
- If ADF personnel deployed with US or UK troops used DU rounds, resulting in possible direct radiation or dust exposure. Exposure to radiation from handling DU rounds has been estimated by the US military to be 0.00001-0.00002 rem/hour, less than the average natural background radiation (0.00003 rem/hour) for tank commanders, gunners and loaders. Realistic exposures based on an estimate of the time spent inside tanks are "likely to be less than 0.1 rem in a year",[135] compared to the five rems per year occupational limit.
- If ADF personnel deployed with US or UK troops were in tanks caught in "friendly fire", resulting in possible shrapnel or dust exposure. About 104 US soldiers were in US vehicles or tanks when they were struck by DU munitions. A further possible 60 soldiers entered the vehicles soon after the attack to rescue occupants.[135] The information from the US military states "this office found no evidence that US military forces engaged any *allied vehicles or personnel* with DU munitions." (our emphasis).[135] We are not aware of any Australian troops that were involved in such "friendly fire" incidents.
- If ADF personnel picked up parts of, or entered damaged or destroyed Iraqi tanks which had been fired on with DU munitions.[15] 50-60% of Danish veterans reported being inside destroyed Iraqi tanks (type of munitions unspecified).[32] This type of exposure was unlikely for the ADF, particularly those deployed on ships before January 1991. ADF troops may, however, have taken tank parts as souvenirs during battlefield tours.

Several items of Iraqi equipment, such as a tank, were shipped to Australia at the conclusion of the deployment. It does not appear likely that these had been subject to a DU round. The tank is still in good working order.

- If any ADF personnel deployed with US or UK troops, were caught up in the aftermath of the Doha depot fire resulting in possible dust exposure.[135]

The US military state that the intake, dose and risk estimates for all US veterans, other than those who were in vehicles struck by DU rounds or who entered these immediately after they were struck, were orders of magnitude below any applicable chemical or radiological guidelines. They conclude that harmful medical effects from DU exposure are not expected where shrapnel is not retained in the body.[135]

The exposure of Australian veterans is likely to have been similar to that of Canadian veterans, also mainly a Naval force. Volunteers from the Canadian forces were tested for urinary uranium. The concentrations of uranium suggest that the volunteers were well within the range observed for non-occupationally exposed individuals.[141] A survey of US veterans found that 16% considered that they had been exposed to DU but found no apparent association between specific exposures and symptoms,[33] that those with and without symptoms reported similar exposure prevalence. In another study 9.5% of US veterans reported exposure to DU.

It appears therefore, that Australian Naval personnel were unlikely to have been exposed to DU, unless from a battle field tour. The only people likely to have been exposed to DU were those ADF personnel deployed with US or UK contingents involved in the special situations described above, or those who took souvenirs from damaged and destroyed tanks hit by DU rounds.

3.11 Infectious disease agents

Exposure to infectious agents includes exposure to biting insects and exposure to possibly contaminated food and water, including consumption of locally sourced food. Australian veterans serving on ships would have been much less likely than land troops to have had these exposures while on board ship. However, the water making process may not have necessarily removed all oil/petroleum products from the heavily contaminated water experienced in the northern Gulf after its deliberate contamination by the Iraqis.

A large number of infectious diseases transmitted by insects are endemic to the Middle East,[142] however, only 40 cases of such infectious diseases were identified among US Gulf War veterans; 32 of these were Leishmaniasis, 7 malaria cases and 1 case of West Nile Fever.[94] One case of Q fever was also reported.[143] There were no reports of sandfly fever among coalition troops.[144]

The most common infectious disease problems were upper respiratory tract infections probably associated with overcrowded living conditions.[88] 84 to 93% of veterans considered that they had been exposed to sources of infectious diseases.[16] Mild travellers' diarrhoea affected 50% of US troops and subsequently local fruit and vegetables were removed from the diet.[25] 48% of US soldiers felt that the latrines were not adequate.[36] US soldiers were provided with bottled water and told to avoid food from street vendors, raw fruit, raw seafood, rare meat and unpasteurised milk. However, there was an outbreak of amoebic dysentery in one US unit.[69]

Between 66 and 82% of both US and UK veterans reported eating locally sourced food.[20, 21, 33, 36] Fewer (21-34%) reported eating food contaminated with smoke, oil or other

chemicals.[20, 33, 46] Between 28 and 31% of US troops used non-US water for bathing, brushing teeth or drinking.[20, 33, 46] A few recalled swimming in local water.[20] In another survey, 2% reported consuming local tap water.[36]

Members of the Australian medical team working in northern Iraq experienced lower rates of diarrhoea than did the British team.[145] This is thought to be a result of better hand and plate washing routines and the use of prophylactic doxycycline treatment.[145]

In summary, Australian Gulf War veterans who were deployed with the Navy appear to have had a low risk of exposure to infectious agents while on the ship either from food, water or from insect vectors. There may have been some risk of these exposures when veterans were in port for rest and recreation but probably no more risk than is usually experienced during deployments in foreign countries. Veterans of Operation Habitat were probably at greater risk.

3.12 Other exposures

Exposure to petroleum products including fuels, paints and solvents could have occurred during the Gulf War. The usual military occupational exposures, eg from cleaning and painting equipment, were experienced in the Gulf, but the usual occupational hygiene procedures were difficult to adhere to in the field.[25] This is illustrated by the reported relative lack of controls over a known hazard, an isocyanate containing paint.[52] In addition, US land based troops were exposed to diesel spread on the ground as a dust suppression agent.[25]

80-91% of UK and US veterans reported exposure to petroleum products.[16, 19-21, 33] 30-64% of veterans reported exposure to paints or solvents,[20, 21, 33] while 57-75% of US and UK veterans reported getting diesel or petrochemicals on their skin[20, 21] although 37% of non-Royal Navy UK veterans resprayed vehicles.[28]

Chemical Agent Resistant Compound (CARC) paint contains hexamethylene diisocyanate which can irritate the eyes and respiratory tract and lead to asthma.[52] (CARC paint has also been reported to contain toluene diisocyanate[71]). The paint was used by one unit of American soldiers and some civilians in the USA prior to shipping vehicles, and in the Saudi Arabian ports of Dammam/Dhahran.[52] 22-48% of veterans reported exposure to CARC paint.[20, 33, 46] It is unlikely that any members of the ADF were involved in respraying vehicles in the Gulf.

Crude oil was released into the Gulf, in Iraq from a loading terminal and a sunken Iraqi tanker and in Kuwait at Mina Al-Ahmady from a battle damaged sea island terminal and from three tankers sunk off Kuwait.[77] This oil moved south along the Saudi Arabian coast and then out to sea.[146] Mine clearance divers, operating along the Kuwaiti coast would have worked in this oil-slick, but ships operating west of 48°E would not have encountered the slick.[146]

86-90% of US veterans reported exposure to vehicle exhaust.[20] Exposure to smoke from tent heaters and waste/excrement incinerations may have occurred for land based members of the ADF, eg those on Operation Habitat, but are less likely to have been experienced by Navy personnel.[28] 51-75% of US veterans[20, 38] and 67% of UK veterans[21] reported exposure to burning trash or faeces. 50-73% of US veterans[20, 33, 41] and 78% of UK veterans[21] reported exposure to exhaust from heaters or generators. 89% of troops recalled exposure to passive smoking.[33]

Sunburn and heat effects were seen during the Gulf War.[36] Heat effects were more severe when NBC suits were used. 13% of US veterans surveyed in one study felt that heat exhaustion, and 13% felt that sunburn were significant problems.[36] There were at least five instances of frost bite among US troops.[69] Both of these effects from temperature extremes are less likely for naval members of the ADF.

3.13 Multi-exposures and recall bias

Many Gulf War exposures can occur together, and therefore attribution of a specific health outcome to a specific exposure is problematic.[16, 21-23, 28, 29, 38, 69, 147, 148] Recall bias can also occur,[149] whereby veterans who report symptoms are also more likely to recall multiple exposures, particularly those considered potentially harmful, than veterans who do not report symptoms.[21, 36] However, the consistency of reported data across military units and between participants who have been randomly selected, and the lack of correlation between many exposure and outcome measures, suggest that recall bias has not been a major problem.[20]

Some veterans in overseas studies are thought to have over-reported certain exposures, eg exposure to chemical weapons and DU. Recall of PB was high on a retest of Gulf War veterans, but there was poor retest agreement for exposure to flea collars, drinking local water, skin contact with petrochemicals, exposure to CARC paint and DU (kappa less than 0.4).[35]

Kroenke *et al* found no apparent association between specific exposures and symptoms. That is, those with and without symptoms reported similar exposure prevalence. However, an increased symptom count for psychological, musculoskeletal and digestive symptoms was associated with the number of self-reported exposures.[33]

In some studies, several exposures have been associated with specific health outcomes. Usually it has not been possible to identify whether the exposures were correlated with each other or whether recall bias occurred. For example, depression has been associated with exposure to solvents, petroleum products, SMOIL, infectious agents, lead, pesticides, radiation, chemical warfare agents and PB. Cognitive dysfunction has been associated with exposure to solvents, petroleum products, SMOIL, lead, pesticides, radiation, chemical warfare agents and PB.[16] Unwin *et al*[21] found that self-reported exposure to SMOIL, protective measures against chemical warfare agents, and possible exposure to chemical warfare agents correlated with several other Gulf War exposures, eg diesel or petrochemical fumes etc, but did not stand out as causal. Proctor *et al*[38] used multiple regression analysis to identify which exposures were associated with health symptoms. This analysis indicated that exposure to pesticides, chemical and biological warfare agents, and smoke from tent heaters were significantly associated with symptoms.

So, if an association is identified between a health outcome and an exposure, caution must be exercised in the attribution of the exposure as causal. Several exposures may in fact be correlated.

3.14 Summary

This review of possible Gulf War exposures for Australian Gulf War veterans has been undertaken to assess which exposures should be considered in this study. Information on the exposures experienced by Australian Gulf War veterans is not well documented. We have had to consider sources such as ships' logs, personal communications, and overseas sources.

Coalition veterans from overseas forces were exposed to a large number of different contaminants and stressors during the Gulf War, described in many papers. Some of these exposures and experiences have subsequently been associated with adverse health outcomes in overseas studies. Members of the ADF are likely to have experienced some but not all of these exposures and the level of exposure are likely to be different from that of overseas forces. For example, members of the Navy who were based on ships were less likely than ground troops to have had significant exposure to many of the contaminants and psychological stressors described in this chapter. Exposures are also likely to have varied for different groups within the ADF. For example, many Air Force Gulf War veterans spent very little time in the Gulf and had little opportunity for exposure there (although a few were stationed in Saudi Arabia). Australian Army personnel deployed in Operation Habitat were based in northern Iraq, not in Kuwait or the Gulf itself.

There are several instances where the specific exposures discussed in this chapter for overseas forces are likely to be different for Australian Gulf War veterans. For example, members of the ADF based on ships are likely to have had much less dust exposure or exposure to biting insects than ground troops. There are also likely to be measurable differences for some of these exposures between ADF members. For example, veterans on HMAS *Adelaide* and HMAS *Darwin* during Damask I could not have experienced SMOIL as they had left the Gulf before the oil well fires started. HMAS *Success* was in the Gulf until January 23rd 1991, which was just after the oil wells were set alight.

At the time of the Gulf War, very few of these exposures were well-documented for Australian Gulf War veterans, and where information is available it is usually anecdotal and subjective. Nonetheless, some objective measurements were made during the Gulf War on SMOIL. These needed to be modelled to estimate the exposure of individuals in the Gulf at the time. Modelling was carried out in the USA to estimate possible exposures of US forces to SMOIL and to sarin as a result of weapon destruction. Exposure to SMOIL and/or chemical warfare agents were both considered unlikely to have been sufficient to cause ill-health among US troops.[42, 45]

Some exposure measures are verifiable, to some extent. For example, the commencement and departure dates of Australian ships are known and can be used in the assessment of possible SMOIL exposure for veterans on these ships. Unfortunately, many other exposures are unverifiable, eg the extent of pesticide exposure, and some exposures may be perceived rather then actual, eg exposure to DU, or exposure to chemical warfare agents based on chemical alarms which responded to other agents such as engine exhaust.[25]

The Gulf War experience, for most Gulf War veterans, is likely to have included the experience of an array of war-related psychological stressors. These may have included fear for personal safety, uncertainty about the potential use of chemical, biological or nuclear weapons, exposure to death and casualties and stress related to uncomfortable environmental conditions. The patterns of psychological stressors may have varied for land-based, compared with ship-based, personnel and for personnel who's deployments ended prior to the air strikes and ground war, compared with those who stayed during and after these battles. There is little published documentation, however, of the pattern of psychological stressors actually encountered by Australian Gulf War veterans.

Many members of the ADF may have experienced exposure to exhaust, petroleum products and solvents, given the nature of their duties in the Gulf. They will also have been immunised and given other prophylactic medicines, although the patterns of these are likely

to be different to those of overseas forces. The ADF use of PB during the Gulf War is not well documented and may have varied between ships.

Given the available evidence from overseas forces, and knowledge about locations and dates of deployment for the ADF, it is unlikely that many members of the ADF were exposed to:

- chemical or biological warfare agents
- DU
- CARC paint.

In addition, there are some exposures that few members of the Navy apart from TGMSE on USNS *Comfort* (but more Army veterans such as those on Operation Habitat) are likely to have experienced. Of course for those individuals concerned, the exposure may have been significant. Such exposures are:

- pesticides including DEET
- sources of infectious disease
- extremes of heat and cold
- exhaust from tent heaters.

The exposures, which appear to be of most relevance in an Australian study, are listed below. Some of these will only be of relevance to a subgroup of Gulf War veterans:

- SMOIL
- dust storms
- psychological stressors
- immunisations
- medications including NAPS
- pesticides including DEET
- solvent exposure

A number of exposures experienced by Gulf War veterans during their Gulf War service will also have been experienced during other active deployments, eg separation from family, or during the rest of their military career, eg exposure to fuel or to smoke from forest fires, or in civilian jobs, eg exposure to solvents. The comparison group in this study will probably also have experienced these types of exposures in their military and civilian lives. Exposures experienced outside the Gulf War need to be assessed and if necessary allowed for in the analysis. This possible confounding effect of non-Gulf War exposures has not been addressed by other studies as far as we are aware.

Despite the evidence suggesting that many of the exposures discussed in this chapter are unlikely for the majority of Australian Gulf War veterans (or are similar to exposures experienced outside the Gulf), it is prudent to aim to assess exposure to these agents as part of the Australian study. This is taken up further in the Cross-Sectional Study Methods, and the Reported Gulf War and Other Exposures chapters.

4. Review of health studies

4.1 Scope of review of health studies literature

There is an enormous published medical research literature on the experiences, exposures and health outcomes associated with deployment to the Gulf War, amounting to several hundred journal article and reports. This literature is being systematically reviewed by teams of the US Institute of Medicine,[25] and more information can be obtained on line at www.nap.edu. Such comprehensive reviews are beyond the scope of this report. In this chapter we provide a tabulation and discussion of the major epidemiological and other studies that are most relevant to the aims of the Australian study.

The sources of information accessed to compile this review were:

- Medline CD-ROM and Current Contents for published medical and scientific literature with the initial search based on literature published over the past 12 years with subsequent sourcing of additional relevant literature from a variety of published sources,
- conference proceedings,
- discussions with key Australian and international researchers,
- correspondence with relevant national and international Defence and veterans organisations, and
- scanning of other internet and world wide web sources.

This review of the health studies relevant to Gulf War deployment and health is based on studies published in the English language only.

4.2 History of Gulf War veterans' health research

The United States (US) had the largest force deployed to the Gulf, involving more than 600,000 personnel, and this was predominantly a land based Army force. For the US military, 17% of deployed personnel were from National Guard and reserve units, and relatively large numbers of women (7%) were deployed.[16] Compared with previous deployments to a war zone, there were fewer casualty deaths (for the US forces there were 148 personnel killed in action and 226 non-combat deaths that were mainly from accidental injuries) and there were no known deaths from infectious diseases.[150] The deployment was, however, characterised by the anticipated threat of the use of biological and chemical warfare weapons by Iraq. In response to this threat, some preparatory measures were taken that were different from other active deployments.

In the months following their return from the Gulf War, US veterans began reporting a variety of symptoms and illnesses that could not be readily explained.[151] Such complaints were soon labelled "Gulf War Syndrome" by the news media.[40] The early studies on the health of Gulf War veterans were undertaken on US veterans. Since these early studies, there have been reports published in the literature, on health problems in Gulf War veterans from several other countries including the United Kingdom, Canada and Denmark, but no published studies of Australian Gulf War veterans.

The complaints affecting Gulf War veterans have been extremely varied. The most commonly reported complaints have been chronic fatigue, rash, headache, muscle and joint aches, difficulty concentrating, forgetfulness and irritability.[17] The Gulf War was not an isolated conflict in this respect. Poorly understood war and post deployment syndromes have

been historically associated with armed conflicts since at least the US Civil War[152] and the British involvement in the Boer War.[153]

Since 1992, there has been a sustained effort internationally to investigate the health complaints of Gulf War veterans. These studies of the health of Gulf War veterans fall into five main groups:

1. Self-reported symptom prevalence, medical conditions and other general health measures surveys (postal or telephone) through cross-sectional studies and factor analyses of Gulf War veterans of the United Kingdom,[21, 28, 154-157] the United States,[16, 20, 38, 73, 158-161] Denmark[32, 162, 163] and an unpublished report of a study of Canadian veterans.[22] Some of these studies included factor analysis, or cluster analysis, of symptoms.
2. Clinical studies or smaller population-based studies or analyses relating to specific health areas or exposures of concern such as vaccinations,[28, 61] respiratory disease,[36, 162, 164, 165] infectious diseases,[150, 166, 167] chronic fatigue and immunological markers,[168, 169] neurological,[31, 157, 163, 170] skin conditions,[171, 172] cancer[173] and psychological health.[174-179]
3. Self-referral clinical evaluation programs and registries such as those established by the US Department of Veterans Affairs (Gulf War Health Registry), the US Department of Defense (Comprehensive Clinical Evaluation Program)[19, 33, 134, 180-182] and the British Ministry of Defence (Gulf War veterans' Medical Assessment Programme).[183-185]
4. Retrospective studies of morbidity including hospitalisations,[107, 173, 186-189] reproductive outcomes including the risk of birth defects,[190, 191] and the study of cancers through hospitalisation[19, 173] and mortality[109, 192, 193] studies.
5. Cohort studies of mortality.[109, 192, 193]

The methodology, health outcome measures, exposure measures and the main findings of the major epidemiological studies that are most relevant to the Australian study are summarised in Table 4.1, with discussion provided in the relevant health outcome sections that follow.

Table 4.1 Cross-sectional epidemiological studies

Study type and study population	Broad categories of exposures assessed	Outcome measures	Main results
Gulf War Illness Research Unit, Guy's, King's, and St Thomas' Medical School, London, UK			
Cross-sectional postal survey of UK servicemen. Random sample of UK Gulf War veterans (n=4248); age and rank matched with Bosnia servicemen (n=4250), and an Era cohort (n=4246) who were serving during the Gulf War but not deployed[21]	Military service and self-reported chemical, environmental, infectious agent, trauma, combat and medical (NAPS and vaccinations) exposures.	Physical health (self-reported symptoms over the last month, with severity scale, and medical disorders), functional capacity (SF-36 health perception and physical functioning subscales), the GHQ, symptom based definitions for CDC multi-symptom criteria for Gulf War illness, posttraumatic stress reaction and fatigue (Chalder Fatigue scale).	Compared with the Bosnia and Era cohorts, Gulf War veterans: - reported symptoms and medical disorders significantly more frequently, - perceived their physical health and ability to be significantly worse, - were more likely than the Bosnia cohort to have substantial fatigue (OR 2.2; 95% CI 1.9-2.6), post-traumatic stress reaction (2.6; 1.9-3.4), psychological distress (1.6; 1.4-1.8) and the CDC multisymptom illness (2.5; 2.2-2.8), - reported potentially harmful exposures most frequently. Multiple exposures showed associations with all of the outcome measures in the three cohorts. Exposures specific to the Gulf were associated with all outcomes. In the Gulf War cohort: - belief of a chemical attack was associated with lowest health perception, CDC multisymptom illness, GHQ and fatigue case criteria, - vaccination against biological warfare (OR 1.5; .3-1.7) and multiple routine vaccinations (1.2; 1.1-1.4) were associated with the CDC multi-symptom syndrome.
Centre for Occupational and Environmental Health, University of Manchester, UK			
Cherry N *et al*. 2001, Part I and II[28, 157] Cross-sectional postal survey of UK service personnel, factor analysis and cluster analysis. Main Gulf War (n=4795) and validation Gulf War (n=4793)	Deployment to other areas of conflict, hospital attendance since 1991, lifestyle factors (alcohol, tobacco). For Gulf War cohorts additional information on deployment dates/location and 14 exposures divided into three groups (exposures outside	95 self-reported symptoms over the last month measured on a visual analogue scale to indicate severity. Two manikins, on which to shade areas of pain or numbness and tingling over the last	Compared with the non-Gulf cohort, Gulf War veterans reported: - nearly all the symptoms about twice as often, with greater symptom severity scores, - symptoms that were rated as particularly troublesome in a similar order, - symptoms suggestive of peripheral neuropathy (12.5% vs 6.8% non-Gulf and widespread pain (12.5% vs 6.8%) more often.

Study type and study population	Broad categories of exposures assessed	Outcome measures	Main results
cohorts were randomly selected within strata from the population deployed to the Gulf between September 1990 and June 1991 and a non-Gulf War cohort (n=4790) from those who were not sent.	the subject's control, prophylactic measures under subject's control, and reactions to conditions in the Gulf as an indication of individual susceptibility).	month, as an indication of widespread pain and possible toxic neuropathy.	Factor analysis identified seven factors that accounted for 48% of the variance. Scores on five factors were significantly worse in Gulf War veterans. Cluster analysis found that most subjects in both groups were in the first two (of six) clusters, representing the healthiest subjects, but that Gulf War veterans were found disproportionately in three clusters with high mean severity scores (23.8% vs 6.5%). The number of vaccinations, days handling pesticides and days exposed to smoke from oil well fires were related to symptom severity score. The number of vaccinations and days handling pesticides were related to the "peripheral factor" that was weighted on symptoms associated with skin and musculoskeletal symptoms, and number of days handling pesticides were related to the "neurological" factor and to symptoms of peripheral neuropathy.
The Iowa Persian Gulf Study Group, Iowa, USA			
The Iowa Persian Gulf Study Group, 1997[16, 160] Cross-sectional telephone interview survey of Iowa Gulf War and non-Gulf War veterans. 4886 study subjects from Iowa randomly selected from one of four groups (Gulf War regular military and National Guard/Reserve, non-Gulf War regular military and National Guard/Reserve) stratifying for age, sex, race, rank and branch of military service with proportional allocation.	Self-reported exposures including solvents/ petrochemicals, oil smoke, infectious agents, psychological, lead from fuels, pesticides, radiation, chemical warfare agents, physical trauma – number, type and duration of exposure and the onset of symptoms immediately following exposure.	137 self-reported symptoms (with a severity scale) and composite measures of 24 medical illnesses and psychiatric conditions present during the past year with an onset during or after the conflict (PTSD, depression, cognitive dysfunction, chronic fatigue, respiratory effects, health related quality of life (SF-36), fibromyalgia, alcohol abuse, anxiety disorders, injuries, reproductive health and cancer).	Gulf War, compared with non-Gulf veterans, had diminished scores for mental and physical functioning and reported: - health problems that they attributed to military service during 1990-1991 more commonly (50% vs 14%), - significantly greater prevalences of 123 (90%) of 137 of symptoms, and none were significantly lower, - significantly higher prevalences of the majority of medical conditions, - symptoms of two or more medical and psychiatric conditions more commonly, - similar rates of conditions that were not expected to be associated with Gulf War service, eg aplastic anaemia, leukemia, injuries, skin blisters or sores. Self reported exposures varied between the regular military and National Guard/Reserve Gulf War groups. Many exposures were related to many of the medical and psychiatric conditions among Gulf War personnel.

Study type and study population	Broad categories of exposures assessed	Outcome measures	Main results
Veterans Health Administration, Department of Veterans Affairs, Washington, D.C.			
Kang, H *et al*. 2000[20] Cross-sectional postal survey of US veterans. Telephone interviews for non-respondents to postal survey. Stratified random sample of 15,000 personnel deployed to the Gulf and 15,000 personnel who were not deployed to the Gulf.	Smoking history, alcohol, and self-reported environmental risk factors. Objective exposure data was not available or not adequately documented to validate self-reported exposure history.	48 self-reported symptoms (including severity and time of onset), chronic medical conditions, activity limitation, self-assessed health status and the use of medical services. Selected self-reported medical conditions and hospitalisations and clinic visits were substantiated through medical records for 4200 respondents.	Gulf War, compared with non-Gulf, veterans had a higher prevalence of: - functional impairment (17.2% vs 11.6%), - limitation of work because of illness or injury within the past 2 weeks (27.8% vs 14.2%), - health care utilisation (50.8% vs 40.5%) or hospitalisation overnight or longer (7.8% vs 6.4%) in the previous year, - significantly lower perception of their health status, - 28 of the 31 self-reported medical conditions (and although the rate differences for some were very small, ie <1%, 12 medical conditions were reported twice as commonly).
Centers for Disease Control and Prevention, Atlanta, Georgia			
Fukuda, K *et al*. 1998[73] Cross-sectional postal survey conducted in 1995 on 3723 active service personnel, irrespective of health or Gulf War status, from an index and 3 comparison US Air Force units. Cross-sectional clinical evaluation of 158/667 Gulf War volunteer veterans from the index unit, irrespective of health status.	Demographics, military service history including Gulf War service, smoking and alcohol.	35 symptoms (with severity and duration scale). Chronic multisymptom illness case definition, ie having 1 or more chronic symptoms (≥6 months) from at least 2/3 categories (fatigue, mood-cognition, musculo-skeletal), and subclassified as a mild-moderate or severe case. Clinical evaluation involved chronic fatigue and psychological assessment, the SF-36, physical examination by a physician assistant, and	Exploratory factor analysis identified three factors “mood-cognition-fatigue”, “musculoskeletal” and respiratory that accounted for 39% of the common variance. Confirmatory factor analysis identified two major factors “mood-cognition-fatigue”and “musculoskeletal”. In Gulf War compared with non-Gulf, veterans: - all current and chronic symptoms (except hay fever) were reported significantly more frequently, - the prevalence of mild-moderate cases and severe cases of the chronic multisymptom illness was higher - 39% vs 14% and 6% vs 0.7% respectively. Severe chronic multisymptom illness was associated with Gulf War service, enlisted rank, female sex, and smoking, and not with number of deployments, time or place of deployment or duties during the war. For the 158 clinically evaluated veterans: - 86 (54%) were mild-moderate cases, 13 (8%) were severe cases and 59/158 (37%) were noncases of chronic multisymptom illness,

Study type and study population	Broad categories of exposures assessed	Outcome measures	Main results
		laboratory investigations (blood, serological, faecal and urine tests).	- no physical examination, laboratory, or serological findings identified cases, and there was a general scarcity of abnormal findings, - veterans who met the case definition had significantly diminished general functioning and well-being, and - current depression was significantly higher among severe and mild-moderate cases than among non-cases (54% and 13% vs 2%) of chronic multisymptom illness.
Epidemiology Division, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas			
Haley *et al*, 1997,[158] Haley and Kurt, 1997[31] Cross-sectional postal survey 249 of the 606 (41%) US Gulf War veterans of the 24th Reserve Naval Mobile Construction Battalion (RNMCB) who were known to have a high prevalence of post-war illness. No control group.	Self-report of war-time exposures to six cholinesterase inhibiting chemical exposures, ie chemical warfare agents, environmental pesticides, pesticides in flea collars or uniforms, DEET-containing insect repellents, PB, other medical, environmental, chemical, and combat stress exposures, smoking, alcohol or cocaine use.	Self-reported 22 current symptoms (with clarifying battery of questions re onset and recency scales) and psychological testing (Personality Assessment Inventory). Two scales (advanced muscarinic and mild muscarinic) of adverse effects from pyridostigmine developed using factor analysis. Factor analysis-derived syndromes and clinically derived US Dept of Defense case definition for Gulf War illness.	Exploratory factor analysis of these symptom scales yielded 6 "syndrome factors" accounting for 71% of the variance in 63 (25%) of veterans. 74/249 (30%) reported no serious health problems and 175/249 (70%) reported having serious health problem that they considered serious since returning from the Gulf. Veterans with Factor 2 "confusion-ataxia" were 12.5 times (95% CI 3.5-44.8) more likely to be unemployed that those with no health problems. 85 (34%) satisfied the case definition for Gulf War illness, and this case definition was strongly associated with Factors 1 "impaired cognition" and 3 "arthro-myo-neuropathy", moderately with Factors 5 "fever-adenopathy" and 6 "weakness-incontinence", but not with Factors 2 "confusion-ataxia" and 4 "phobia-apraxia". A clinically significant score on the Somatic Complaints Scale was found in 30 (48.4%) of those with one or more of the factors. This psychological profile was similar to those in general medical patients who have chronic medical illnesses, and differed from posttraumatic stress disorder, depression, somatoform disorder and malingerer's profile.

Study type and study population	Broad categories of exposures assessed	Outcome measures	Main results
The Danish Gulf War Study			
Ishøy, T *et al*. 1999[162] Cross-sectional survey of 821 Danish subjects deployed to the Gulf area, 95% of whom had been engaged in peacekeeping operations after the war, and 400 randomly selected age-, gender- and professionally matched controls.	Self-reported demographics; physical, chemical, biological, vaccination, psychosocial (work conditions and stress) exposures including specific events, psychosocial work conditions, psychological stress, exposures and experiences during Gulf deployment, tobacco, alcohol and major life events.	Self-report of work injuries, medical conditions, family diseases, use of medicines and health services, physical activity, and symptoms during the preceding 12 months (including timing of onset). Physician interview with medical examination, height, weight, BP, ECG, spirometry, computerised coordination test (CATSYS) and urinalysis. Laboratory tests including haematological tests, IgG, IgA, IgM, IgE, liver function tests, cholesterol and triglycerides.	Gulf War, compared with non-Gulf, veterans experienced: - neuropsychological symptoms significantly more frequently ($p < 0.05$), - gastrointestinal symptoms more frequently, with significant differences for 8/14 symptoms, although the differences did not persist when subjects who had been in other international missions were excluded, - diseases and symptoms related to the skin or allergy significantly more frequently, and the effect was more pronounced for eczema and other forms of skin problems, - higher prevalence for symptoms or conditions which first appeared during or after the Gulf War, but not for symptoms which first appeared before August 2 1990, - a larger proportion having one or more ICD-10 diagnoses at the examination (80.8% vs 71% $p=0.002$) and 260 subjects (38%) had one or more diagnoses that could be related to their stay in the Gulf. Although significant differences between groups were found for the parameters of platelets, eosinophils, IgM, plasma amylase and plasma creatinine, all laboratory parameters were within the range of normal values for both groups.
Canadian Forces involved in the Gulf, Goss Gilroy Inc, Ontario, Canada			
Goss Gilroy Inc, Management Consultants, Ontario, Canada, 1998[22] Cross-sectional postal questionnaire survey Canadian Gulf War veterans (n=3113 of 4262) and a control group of military personnel who served in other locations at the	Sociodemographic factors, lifestyle factors, immunisations, medical, chemical, environmental, combat exposures, military service history including other deployments.	Personal functioning including health services utilisation and use of medication, general health perception and social functioning, pain, neuropsychological and fatigue symptoms, posttraumatic stress disorder (PCL-M),	Gulf War, compared with non-Gulf War, veterans reported: - more health problems that were both of short and long term duration, single illnesses or combined health outcomes, - a lower pre-1990 prevalence rate for selected long term medical conditions, but a higher incidence of such conditions during 1991-94, that fell to steadier levels after 1994, - higher numbers of children with birth defects for all three periods (before, during and after the Gulf War), but both Gulf War veterans and control group rates were within general population expectations.

Study type and study population	Broad categories of exposures assessed	Outcome measures	Main results
time of the Gulf War (n=3439 of 5699). Gulf War veteran and control findings were also compared with the general population through the 1990 Ontario Health Survey.		psychological disorders, long term health problems, medical conditions, women's health, and reproductive outcomes.	- higher prevalence of many different reported health events that could not be explained by participation in other deployments. Psychological stresses and trauma were associated with all combined health outcomes (except alcohol abuse). Income and rank were important confounding factors.

4.3 Symptoms

Symptom prevalence surveys have been used as a health outcome measure in many of the cross-sectional, epidemiological studies and have explored the relationship between symptoms, or specific groups of symptoms such as neuropsychological or cognitive symptoms, and exposures.[16, 21, 22, 73, 157-160, 162, 194, 195] The most consistent finding in the cross-sectional studies has been an increased reporting of multiple symptoms by Gulf War veterans in comparison with their non-Gulf comparison groups.[16, 21, 22, 73, 157-159, 162, 195] The ordering of symptoms most commonly reported by the Gulf War veterans and the comparison groups has been very similar,[21, 157] as has the ordering of symptoms most commonly reported by the Gulf War veteran groups in different studies.[20] In addition to their use in the comparison of the prevalences of self-reported symptoms, self-reported symptoms have also formed the basis of factor analyses undertaken by some research groups (see section 4.4).

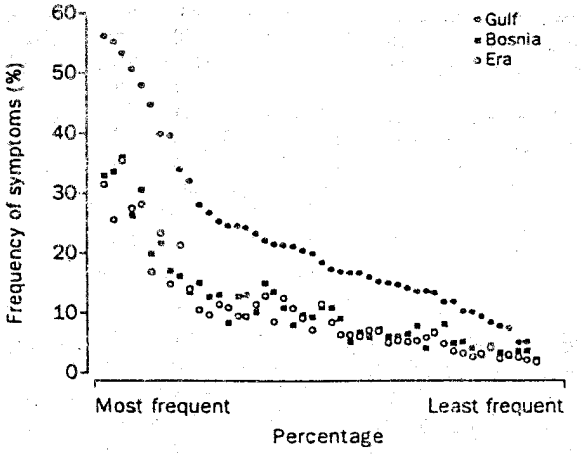
The prevalence ranges for symptoms commonly reported in the major epidemiological studies, in the order of prevalence of the 15 symptoms most frequently reported by UK Gulf War veterans in the study by Unwin *et al*, [21] were:

- feeling unrefreshed after sleep (47-56.1%),[20, 21]
- irritability or outbursts of anger (25-55.2%),[20, 21, 160]
- headaches (23-54%),[20, 21, 160]
- fatigue, tiredness, lacking in energy, needing to rest more or feeling unusually sleepy/drowsy (27-50.7%),[20, 21, 160]
- sleeping difficulties (26-48.0%),[20, 21, 160]
- forgetfulness or problems with memory (21-44.9%),[21, 160]
- loss of concentration or concentration difficulties (35-39.7%),[20, 21]
- flatulence or burping (34.1%),[21]
- pain without swelling or redness in several joints (32.2%),[21]
- feeling distant or cut off from others (28.1%),[21]
- avoiding doing things or situations (26.8%),[21]
- chest pain or tightness in chest (21-25.3%),[20, 21]
- tingling in fingers and arms or numbness or tingling in parts of body (24.7-33%),[20, 21, 160]
- night sweats or hot or cold spells, fever, sweats or chills (18-24.6%).[20, 21, 160]

Sensitivity to at least one everyday chemical was reported by 28% of Gulf War veterans, 14% of the Era veterans and 13% of the Bosnia veterans.[196]

This increased reporting of symptoms by UK Gulf War veterans is aptly illustrated in Figure 4.1 (reproduced with permission of Prof Simon Wessely).

Figure 4.1 Symptoms by deployment for UK veterans, Unwin et al [21]



The severity of symptoms and the disability related to the reporting of symptoms have also been studied. Gulf War veterans were nearly twice as likely to meet the CDC multisymptom illness case definition {odds ratio (OR) = 2.5; 95% CI 2.2-2.8 and OR 2.9; 95% CI 2.6-3.3) compared with Bosnia or Era veterans respectively, in the UK study.[21] Cherry *et al*[157] found that the severity of symptoms was greater in Gulf War veterans, with a mean severity score of 3.0 that was significantly greater than that of the non-Gulf cohort's score of 1.7 ($p<0.001$). Lower symptom severity scores were found in veterans less than 25 years of age, officers, serving members and those who had been in the Army and Air Force. Symptom severity scores were at least twice that of the non-Gulf cohort for 14 symptoms, and these were predominantly neuropsychological in nature. Using cluster analysis[197] (in this case clustering together subjects who have similar clinical profiles), with each subject assigned to one of six clusters, Cherry *et al*[157] found that most subjects in both the Gulf War veteran and comparison group were in the first two clusters, representing the healthiest subjects. However, Gulf War veterans were found disproportionately in three clusters with high mean severity scores (23.8% Gulf; 9.8% non-Gulf). Although Gulf War veterans self-reported more psychological morbidity, substantial fatigue, non-specific physical symptoms and poor perception of physical health and ability compared with UK servicemen who were not deployed to the Gulf, the disability experienced was not severe.[21]

Increased reporting of, or severity of, symptoms has been associated with a number of different Gulf War exposures. For example, the number of vaccinations, days handling pesticides and days exposed to smoke from oil well fires, reported days of use of NAPS tablets and insect repellent, feelings that life was in danger, need for medical attention while in the Gulf and side effects from NAPS tablets were all associated with a higher symptom severity score.[28] The individual factors, obtained from factor analysis (defined below), were related to fewer exposures than the symptom severity scores. Two exposures outside the subject's control (number of vaccinations and days handling pesticides) were related to the 'peripheral' factor and pesticides to the 'neurological' factor. Reported days of use of insect repellent were related to scores on the 'peripheral', 'respiratory' and 'appetite' factors. Those who thought their life had been in danger scored higher on the 'psychological' factor, and those who had received medical attention and or side effects from nerve agent prophylaxis scored higher on the 'gastrointestinal' factor. Exposure to smoke from oil well fires was not related to scores on the 'respiratory' factor.[28]

Specific places of service within the Gulf War theatre (Iraq, Saudi Arabia, Kuwait) were significantly associated with higher prevalence of depression, cognitive dysfunction and fibromyalgia compared to service in other parts of the Gulf War theatre.[16]

The associations of pyridostigmine bromide (PB or NAPS) with both general and specific health effects were considered in a number of studies. Half of a population of soldiers taking PB under wartime conditions noted gastrointestinal symptoms and increased urinary frequency and urgency. One percent of soldiers believed that the effects were severe enough to warrant medical attention and about 0.1% were so severely affected that the PB was discontinued.[92] A similar study suggested that PB did not affect soldier's performance in a desert environment.[198] Symptoms experienced by soldiers taking PB during war were generally mild and anxiety was thought to account for some symptoms. The symptom frequency was not compared to the frequency reported by soldiers not taking the medication however.[199] A study of female Gulf War veterans who responded to a survey found that long term adverse health was associated with the use of more than 10 PB pills.[200] Decreased hand strength was not associated with PB in a study of Gulf War veterans.[201]

Self-perception of general health and well-being has been found to be significantly lower in Gulf War veterans compared with non-Gulf veterans,[16, 20, 21] and in severe and mild-moderate cases of a chronic multisymptom illness,[73] with fewer Gulf War veterans describing their health as excellent or very good.[20]

Although Danish Gulf War veterans were predominantly deployed after the war in peacekeeping missions, they exhibited a pattern of symptoms, except for musculoskeletal symptoms, consistent with the findings among US Gulf War veterans. This was thought to indicate the existence of some common risk factors independent of war action.[162] In this study only minor differences were found between the Gulf War veteran and comparison group on haematological, serological and biochemical test results, and only a few test results (platelets, eosinophils, IgM, amylase and creatinine) were different between the two groups.

Some participants have attributed illness in the post war period to service in the Gulf. In a study of 249 of the 606 US Gulf War veterans of the 24th Reserve Naval Mobile Construction Battalion (RNMCB) who were known to have a high prevalence of post-war illness, 175 (70%) participants reported having serious health problems that most attributed to the war, and 74 (30%) reported no serious health problems.[158] Doebbeling *et al*[160] found that one half (50%) of Gulf War veterans, while only 14% of non-deployed controls, reported health problems that they attributed to military service during 1990-1991.

4.4 Factor analysis

The statistical technique known as factor analysis has been used in the context of Gulf War health research to investigate whether non-specific health symptoms which Gulf War veterans report more commonly than their non-Gulf comparison groups constitute a new disorder or syndrome. A syndrome, by definition, is a "symptom complex in which the symptoms and/or signs coexist more frequently than would be expected by chance on the assumption of independence".[202] Rare symptoms that could be a specific marker for an illness may be missed if the approach assumes that common symptoms are clinically important.[154] Factor analysis of self-reported symptoms from cross-sectional prevalence surveys has been undertaken by a number of research groups in the UK[154, 157] and the US.[46, 73, 158, 160, 194]

(Exploratory) factor analysis is a generic term for a "set of statistical methods for analyzing the correlations among several variables in order to estimate the number of fundamental dimensions that underlie the observed data and to describe and measure those dimensions".[202] In the context of Gulf War health research, factor analysis has been used as an analytical approach to identify whether the correlations between a set of observed variables, for example self-reported symptoms can be explained by a few latent, unobserved variables called "factors".[154] Once the optimal number of factors has been determined, a 'label' is given to each of the factors that the researchers think most aptly describes, in clinical terminology, the nature of the symptoms that load onto that factor.

On the basis of factor analysis of symptoms reported in a study of 249 US Naval personnel who served in the Gulf War, Haley *et al*[158] identified six factors labelled Factor 1 "impaired cognition", Factor 2 "confusion-ataxia", Factor 3 "arthro-myo-neuropathy", Factor 4 " phobia-apraxia", Factor 5 "fever-adenopathy" and Factor 6 "weakness-incontinence". These factors accounted for 71% of the variance, in 63 (25%) of the 249 veterans in the sample. There was some overlap of the factors. The three factors of "impaired cognition", "confusion-ataxia", and "arthro-myo-neuropathy" represented strongly clustered symptoms; whereas the three factors of "phobia-apraxia", "fever-adenopathy" and "weakness-incontinence" represented weakly clustered symptoms and mostly overlapped with the factors of "confusion-ataxia", and "arthro-myo-neuropathy'

Ismail *et al*[154] identified three factors labelled "mood", "respiratory system" and "peripheral nervous system" in the Gulf War cohort, that together accounted for 20% of the common variance, and fitted well when fitted separately to the Bosnia and Era cohorts in a confirmatory factor analysis. Confirmatory factor analysis is a technique that is complementary to exploratory factor analysis and is used to investigate whether an a priori postulated factor structure provides an adequate model for explaining the correlation among the observed variables in a (new) set of data.[203] The postulated factor structure is often generated from the results of a prior exploratory factor analysis.

The above study group did not consider that their findings supported the existence of a unique Gulf War syndrome. The fit of the factor structure proposed by Haley *et al*[158] was poor in all three cohorts. Several explanations were proposed including the use of an approximation of Haley's model, incorrect factors and variance due to the use of multiple symptoms in a small unrepresentative sample and no control group to compare the factor structure against.

Knoke *et al*[194] applied factor analysis to the symptoms reported in a survey of active duty US Naval personnel that were considered to be similar to the group studied by Haley[158] as well as a military comparison group. Factor analysis applied to the Gulf War veterans data yielded five factors (three deriving from the Hopkins Symptom Checklist, one suggesting clinical depression, and one containing symptoms commonly reported by Gulf War veterans) that were similar to those yielded by the non-deployed veterans. Gulf War veterans reported similar clusters of symptoms and illness to the non-Gulf veterans, but with greater frequency.[158] The researchers concluded that factor analysis did not identify a unique Gulf War syndrome.[194]

Cherry *et al*[157] , used factor analysis to identify seven factors that accounted for 48% of the variance (in the Gulf War group). Scores on five of the factors ("psychological", "peripheral", "respiratory", "gastrointestinal" and "concentration") were significantly higher in the Gulf War cohorts compared with the non-Gulf War cohort, reflecting the increased severity of symptoms. One factor, "appetite", was significantly lower, and one factor,

"neurological", was similar, in the Gulf War cohorts compared with the non-Gulf War cohort.[157]

Doebbeling *et al*[160] undertook factor analysis of symptoms reported in a cross-sectional telephone interview survey of Iowa Gulf War and non-Gulf War veterans. Factor analysis on a random subset of the deployed veterans to identify latent patterns of symptoms was compared with those obtained from a validation sample of deployed veterans and non-deployed controls. Factor analysis identified three replicable symptom factors in the deployed veterans labelled "somatic distress", "psychological distress", and "panic" that were highly replicable in the non-deployed comparison group. The three factors accounted for similar proportions of the common variance among the deployed veterans (35%) and non-deployed controls (30%).[160]

Kang *et al*[46] performed a factor analysis of 47 symptoms from a mail survey of 15,000 Gulf War veterans and 15,000 non-Gulf War veterans. The four and five factor solutions for Gulf War and non-Gulf War veterans were virtually identical, providing evidence against a unique syndrome among Gulf War veterans. However, their six factor solution displayed a cluster of four symptoms in one factor (blurred vision, tremor/shaking, loss of balance/dizziness, speech difficulty) in the Gulf War veterans not found in the non-Gulf War veterans. The authors concluded the possible existence of a syndrome related to Gulf War deployment. However, evidence for the need for a six-factor solution (beyond that of a three, four or five factor solution) was not strong, and in fact the editor of the journal in which the article was published vehemently disagreed with the authors' conclusions in a footnote to the article.

Exploratory factor analysis by Fukuda *et al*[73] identified three factors "mood-cognition-fatigue", "musculoskeletal" and "respiratory" that accounted for 39% of the common variance. A replication factor analysis identified two major factors, "mood-cognition-fatigue" and "musculoskeletal". These researchers reported a chronic multisymptom illness that was significantly associated with deployment to the Gulf War, but was not associated with specific Gulf War exposures and which also affected non-deployed personnel.[73] The prevalence among Gulf War veterans of mild-moderate (39% vs 14%) and severe cases (6% vs 0.7%) was higher than among non-Gulf veterans. Severe illness was associated with Gulf War service, enlisted rank, female gender, and smoking. Fifty-nine clinically evaluated Gulf War veterans (37%) were noncases, 86 (54%) mild-moderate cases, and 13 (8%) severe cases; and there were few abnormal findings identified through these clinical examinations. No physical examination, laboratory, or serological findings identified cases. Major depression was more common among Gulf War veterans after deployment than before, and prevalence of current depression was significantly higher among severe chronic multisymptom cases (54%) and mild-moderate cases (13%) than among non-cases (2%). Four subjects (all chronic multisymptom cases) met the criteria for somatisation disorder. Eight subjects met all criteria for chronic fatigue syndrome, and of these 7 (54%) were severe cases and 1 (1%) was a mild-moderate case. Veterans who met the case definition had significantly diminished functioning and well-being as measured by the SF-36.[73]

There were similarities between the "mood-cognition" and "respiratory" factors of Ismail *et al*[154] and two of the three factors of the factor structure of Fukuda *et al*,[73] and the "peripheral nervous system" and "respiratory" factors were similar to the "neurological/conversion" and "autonomic" factors of the four factors identified in an international primary care study.[204]

Factor analysis has limitations. The findings of complex modelling procedures need to be interpreted with caution.[154] The identification of factors through factor analysis does not in

itself imply that these factors represent a recognised psychiatric or physical disorder or dysfunction, and validation against criterion measures is required.[205] Factor analysis alone cannot definitively establish a new illness when applied to self-reported symptoms, and a similarity of symptomatology between groups is not sufficient to rule out a separate illness.[205]

Generally, the findings between studies that have employed factor analysis, and which have included a control group, have been consistent,[73, 154, 158, 194] in that they have not supported the concept of a unique Gulf War syndrome.

4.5 Medical conditions

Self-reported medical conditions have been investigated as health outcomes in many of the cross-sectional epidemiological studies.[16, 21, 22, 73, 157-160, 162, 194, 195] The pattern of self-reporting of medical conditions has been similar to that of symptoms, although not as consistent or marked, with Gulf War veterans reporting many,[16, 20] or all,[21] medical conditions more frequently than non-Gulf veterans. Some medical conditions have been reported twice as commonly by Gulf War veterans as by non-Gulf veterans.[20]

There are some similarities in the order of frequency of medical conditions between studies. Medical conditions commonly reported by UK and US veterans,[20, 21] in the order of prevalence for the 15 most frequent medical conditions reported by UK Gulf War veterans in the study by Unwin *et al*,[21] (the second figure, where given is from the Kang *et al* study[20]) were:

- back disorders (35.7%),
- hay fever (21.6%),
- dermatitis (21.3-25.1%),
- sinus disorders or sinusitis (19.6-38.6%),
- migraines (16.5-18.1%) %),
- diseases of hair or scalp or hair loss (16.5-16.9%),
- ear infection (12.3%),
- loss of hearing (11.8%),
- arthritis or rheumatism (9.7-22.5%),
- sexual problems (9.0%),
- high blood pressure or hypertension (8.8-11.4%),
- eczema or psoriasis (7.7-7.8%),
- asthma (4.7-6.5%),
- bronchitis (4.4-11.2%),
- disease of genital organs (3.8-4.8%).

The Iowa Persian Gulf Study Group[16] found that Gulf War veterans more commonly reported symptoms of two or more medical and psychiatric conditions (14.7% vs 6.6%) than the non-deployed comparison group. Gulf War veterans had diminished scores for mental and physical functioning on the SF-36; and reported significantly higher prevalence of symptoms of medical or psychological conditions such as depression (17.0% vs 10.9%), PTSD (1.9% vs 0.8%), chronic fatigue (1.3% vs 0.3%), cognitive dysfunction (18.7% vs 7.6%), bronchitis (3.7% vs 0.7%), asthma (7.2% vs 4.1%), fibromyalgia 19.2% vs 9.6%), alcohol abuse (17.4% vs 12.6%), anxiety (4.0% vs 1.8%,), and sexual discomfort (1.5% vs

1.1%) compared with non-Gulf War veterans. In nearly all cases, larger differences between Gulf War and non-Gulf War veterans were observed in the National Guard/Reserve comparison.

Chalder *et al*[156] found that 17.3% (95% CI 15.9-18.7%) of respondents to a UK Gulf War veterans study[21] believed they had Gulf War syndrome. Belief in having a "Gulf War syndrome" was associated with the veteran having poor health, not serving in the Army at the time of responding to the questionnaire, and having a high number of vaccines before deployment to the Gulf; but was most strongly associated with knowing another person who also thought they had Gulf War syndrome. Those who believed they had Gulf War syndrome were more fatigued, more distressed, more likely to have posttraumatic stress reaction and more likely to fulfil the CDC criteria for multisymptom illness. They had worse health perceptions, were more physically disabled and reported more symptoms than those who did not believe they had Gulf War syndrome. Of those who believed they had Gulf War syndrome, 462 (90%) fulfilled the CDC multisymptom criteria for Gulf War illness; although, when disability was considered, only 221 (43%) of the veterans who believed they had Gulf War syndrome were symptomatic and disabled according to the criteria. Of the participants who believed they had Gulf War syndrome, 444/513 (86.5%) attributed a change in functioning to their service in the Gulf.

Belief of exposure to a chemical attack was associated with low health perception (Gulf War cohort OR 2.4; 95% CI 1.8-31.2), CDC multisymptom illness (OR 2.6; 95% 1.9-3.5), the GHQ case criteria (OR 2.0; 95% CI 1.5-2.5) and fatigue case criteria (OR 2.2; 95% CI 1.7-2.9).[21] Unwin *et al*[21] found that multiple exposures showed associations with all six health outcome measures in the Gulf War, Bosnia and Era cohorts. The Iowa Persian Gulf Study group[16] also found that, among Gulf War personnel, most of the self-reported exposures were significantly related to many of the medical and psychiatric conditions.

4.6 Demographic and lifestyle factors

Ismail *et al*[155] examined the relationship between Armed Forces occupational factors and ill-health after accounting for sociodemographic and lifestyle factors. This study found that rank was the main occupational factor associated with psychological and physical ill-health. Higher rank was significantly and inversely related to psychological and physical ill-health (test of trend: GHQ, p=0.004; posttraumatic stress reaction, p=0.002; fatigue, p=0.015; CDC multisymptom illness case, p=0.002). Privates were around 20% more likely to report ill-health than non-commissioned officers and around 70% more likely to report ill-health than officers. There was a small but significant trend between educational attainment before joining the Armed Forces and fatigue (p=0.036), and a significant linear trend between smoking (but not alcohol) and all health outcomes. Those who had left the services (57% of veterans) were more likely to have fatigue (OR 1.4; 95% CI 1.2-1.7), CDC multisymptom illness (OR 1.8; 95% CI 1.5-2.3), psychological distress (OR 1.6; 95% CI 1.3-1.9) and posttraumatic stress reaction (OR 2.5; 95% CI 1.9-3.2); and ex-service Gulf veterans were around two times more likely to report psychological and physical ill-health. Pre-deployment training and post-deployment leave did not seem to be associated with ill-health in Gulf War veterans. Marital status and smoking were associated with psychological ill-health. The authors proposed that rank may be a proxy for socioeconomic status rather than a proxy for environmental or chemical exposures experienced during the Gulf War.

Cherry *et al*[157] reported no excess in the use of alcohol or tobacco by Gulf War veterans. Kang *et al*[20] reported that a significantly higher proportion of Gulf War veterans were

smokers compared with non-Gulf veterans (34.7% vs 29.9%), but that a similar proportion of both study groups drank alcoholic beverages (76.6% vs 74.1%). In neither of these studies were these differences thought to be large enough to explain differences in health perceptions and symptom reporting.

4.7 Psychological health

Historically, many studies have shown that the experience of war, and the subsequent transition from military to civilian life, can have legacies that manifest themselves in a variety of physical and psychological health problems.[152] The adverse effects of combat experience through WWII and into the 1950s were described by terms such as combat fatigue,[206] shell shock,[207] battle exhaustion[208] and combat stress reaction.[209] The related symptoms can be described in contemporary terms under a syndrome known as posttraumatic stress disorder, which is a type of anxiety disorder (American Psychiatric Association, 1996). Symptoms include emotional numbing, behavioural changes and re-experiencing of similar or related events such as flashbacks. The prevalence of posttraumatic stress disorder has been demonstrated to be as high as 50% in former WWII prisoners of war[210] and 40% in wounded veterans of the Vietnam War.[211] Depression, other anxiety disorders and substance abuse have also been reported to be elevated in combat-exposed populations.[212]

Many international studies have investigated the psychological health of veterans of the Gulf War. These studies have often included self-selected populations[19, 178, 184] or relatively small numbers of subjects.[213-215] Such studies are therefore limited in the generalisability of their results to the broader Gulf War veteran population. Further, many of the larger cross-sectional studies have relied solely on quite brief, self-administered questionnaires for the collection of psychological health data.[21, 22, 28, 157] Some studies have incorporated telephone interviews[16, 20, 160] but no large, cross-sectional studies have included comprehensive and face to face psychological examinations.

Despite the limitations of the existing Gulf War literature, higher than expected rates of psychiatric conditions and unexplained physical symptoms in Gulf War-exposed groups have been consistently demonstrated. In their review of 20,000 US Gulf War veterans evaluated through the CCEP, Joseph *et al*[19] reported that 18.3% of subjects received a primary diagnosis of an ICD-9 mental disorder. This ICD-9 category represented the second most frequent primary diagnosis, with only diagnoses of 'diseases of the musculoskeletal system and connective tissue' being more common at 18.6%. The third most common broad diagnostic category was 'symptoms, signs and ill-defined conditions' which represented 17.8% of primary diagnoses and 32.6% of secondary diagnoses. Somatic symptoms are commonly coded in this category, and are often either simply lacking a physical explanation or are thought to be related to psychological factors.[33, 216] Among veterans with a primary diagnosis of "mental disorders", 19% had tension headache, 17% depressive disorder not elsewhere classified, 15% prolonged posttraumatic stress disorder, 8% major depressive disorder, (single episode) and 7% adjustment reaction.[19] Mental disorder was also the most common category of principal diagnoses in an analysis of combined collected data from the US Department of Veterans Affairs Persian Gulf Veterans' Health Registry and the Department of Defense's CCEP, with 14.7% of subjects categorised as having an ICD-9 mental disorder.[182]

In their study of hospitalisation amongst 1,984,996 US active duty personnel, Dlugosz *et al*[217] found Gulf War service to be associated with significantly greater risk for acute

reactions to stress. Major depression has also been shown to be more common among US Gulf War veterans after Gulf War deployment than before.[73]

Amongst UK servicemen, Gulf War service has been associated with significantly increased psychological distress as measured by the GHQ-12,[218] and significantly higher levels of symptoms consistent with posttraumatic stress reaction,[21] in Gulf War veterans when compared with non-Gulf War comparison groups. UK servicemen who served in the Gulf War are also at least twice as likely to report symptoms of poor memory, concentration difficulties, feelings of irritation without reason, sudden mood change, feelings of anger which were difficult to control and indecisiveness, when compared with similar UK servicemen who did not deploy to the Gulf War.[157]

Health care provider diagnosed PTSD was reported to more prevalent in Canadian veterans of the Gulf War than in the non-Gulf War comparison group.[22] This study also showed that symptoms suggestive of PTSD, minor depression, major depression, chronic dysphoria and anxiety were significantly more prevalent in Canadian Gulf War veterans than in the comparison group. Further, Danish veterans of the Gulf War have been shown to report non-specific psychological symptoms such as memory and concentration difficulties, sleep disturbances and agitation, significantly more frequently than a Danish service comparison group.[162]

In general, Gulf War studies have been limited in their investigation of the possible causes of psychological distress in Gulf War veterans. Only a few studies, for example, have specifically investigated the association between deployment-related or combat-related stressors and the subsequent patterns of psychological morbidity in Gulf War veterans.[177-179] In this report, a description of the wide range of possible Gulf War related stressors can be found at chapter 3.

Few specific characteristics of Gulf War service, or exposures relating to the Gulf War deployment, have consistently been associated with the increased risk of psychological morbidity. Ismail *et al* (2000)[155] reported an inverse relation between higher rank and psychological ill-health in 3297 Gulf War veterans of the UK. This study found no further association between psychological ill-health and type of service, combat arm or reservist status. An earlier study with the same population reported strong associations between posttraumatic stress and Gulf War related psychological stressors including injury, seeing maimed soldiers and dismembered bodies, dealing with prisoners of war and the sounding of chemical alarms.[21] Of these, however, only the association between posttraumatic stress and the sounding of chemical alarms was unique to the Gulf War veteran study group.

McCarroll *et al*[14] reported increased somatic symptoms in Gulf War mortuary workers who handled dead bodies and McDuff *et al* (1992)[178] reported that battle intensity, best measured by the number of soldiers wounded or killed during each day of combat, was the best predictor of psychological distress in soldiers treated for "Army stress". These researchers also listed individual factors such as training, fitness, combat experience, hydration, sleep, food, soldier quality, stability of personal life, and unit factors such as morale, leadership, cohesion and training as important predictors of stress casualties.[178] Combat severity was also implicated by Sutker *et al*[177] who found that Gulf War veterans with PTSD scored higher on a measure of severity of war-zone exposure. These researchers also found that veterans with PTSD also differed on personal traits unrelated to the Gulf War deployment when compared with veterans without PTSD. PTSD cases demonstrated lower levels of family cohesion, family expressiveness, problem focused coping, coping using social support,

hardiness, Shipley IQ, and social support and higher levels of wishful thinking, avoidance and self coping by blaming.

Gulf War veterans who served in ground war support occupations were found to be at greater risk for post-war drug-related disorders and male Gulf War veterans who served in ground war combat occupations were at higher risk for alcohol-related disorders.[217] Hotopf *et al*[61] found that multiple vaccinations received before deployment were associated with symptoms of PTSD, but vaccines received during deployment were not associated with this health outcome. The US Persian Gulf Veterans Coordinating Board found that nearly half of 17248 ill or concerned veterans who reported neuropsychological complaints had been Reservists or National Guard personnel, a population that represented only 17% of US troops deployed to the Gulf.[17] No other distinctive demographic, exposure or geographic risk factor could be linked to this self-referred population. Joseph *et al*[19] reported that mental disorders were more common among younger participants, however there were no major differences across ICD diagnostic categories in the percentage of participants reporting various exposures, including exposure to combat or combat-related deaths.

There are no comprehensive investigations of psychological health or deployment related stressful events reported in the scientific literature in relation to Australian veterans of the Gulf War. However, in a report compiled by the Australian Gulf War veterans' Association, for submission to the Commonwealth Minister for the Department of Veterans' Affairs, Australian veterans claimed to be experiencing similar psychological health problems to those experienced by veterans of other countries whom they served alongside.[219] Reported symptoms, which might be related to psychological disorders, include nightmares, night sweats and other sleep problems, short term memory problems and difficulty concentrating, emotional problems including irritability, mood swings and uncontrolled anger, depression, suicidal thoughts, episodes of panic and anxiety, heart palpitations and shortness of breath, difficulty swallowing, loss of sexual libido, increased startle response, low tolerance for noise and low tolerance for stress. Such anecdotal reports need to be interpreted with some caution, however they do provide some qualitative data which are helpful in deciding which psychological health outcomes to include in an epidemiological study. Australian Gulf War veterans also reported facing many stressful events during their deployment to the Gulf. These are described in chapter 8.

In the current scientific literature, the overall picture of psychological morbidity in Gulf War veterans and related exposures is a complex one. Common themes appear in findings of increased depressive, anxiety and PTSD-related symptoms, alcohol or substance misuse and multiple non-specific psychological symptoms. There is some evidence, though not consistent, that these psychological health outcomes are possibly associated with levels of combat severity and unit resourcing, combined with levels of rank or seniority, youthfulness, training, combat experience and personal resourcefulness.

4.8 Respiratory health

Acute respiratory infections caused widespread minor morbidity among US troops during Operation Desert Shield and Operation Desert Storm, particularly during periods of initial deployment and crowding. An increase in community acquired pneumonia was also reported among British troops.[150]

Richards *et al*[164] conducted an epidemiological study of 2598 male US personnel. These personnel were stationed for an average of 102 days in different conditions in various geographic areas in north east Saudi Arabia during Operation Desert Shield before the oil

fires in Kuwait were started. Respiratory tract complaints were common in these personnel, with a sore throat reported by 34.4%, persistent rhinorrhoea reported by 15.4%, and cough reported by 43.1% of the participants. In only 1.8% of participants were these respiratory complaints severe enough to prevent them from performing their duties. Numerous respiratory pathogens were identified in 68 patients from whom blood and throat swab specimens were collected. A potential bacterial aetiology was found in very few patients {*N.meningitidis* (4), *S.pneumoniae* (1), *H.influenzae* (1), *M.pneumoniae* (1)} and four viruses were also identified in blood and throat swabs.[164]

Personnel who were deployed for longer periods of time were more likely to report respiratory problems than personnel deployed for shorter periods.[164] There was no relationship between age or rank and respiratory complaints. Subjects with a history of respiratory disease (primarily mild asthma and bronchitis/emphysema) (6%) and current cigarette smokers (37%) had a significantly higher prevalence of respiratory complaints. There was a trend towards increased risk for complaints of sore throat and cough with less exposure to the outdoor environment and a trend towards increased risk of complaints of chronic rhinorrhoea with more exposure to the outdoor surroundings. Crowding and recirculation of indoor air containing respiratory pathogens was thought to contribute to the former finding and exposure to outdoor air pollutants or allergens was thought to contribute to the latter finding.[164]

For the period following the burning of the oil wells, a survey of Kuwaiti clinics showed an increase in the rate of presentation for upper respiratory tract irritation but no observed increase in visits for respiratory infections or asthma.[83]

In cross-sectional studies since the time of the Gulf War, US Gulf War veterans have reported significantly higher prevalence of respiratory conditions than non-Gulf comparison groups. Iowa Gulf War veterans reported a significantly higher prevalence of symptoms of asthma (7.2% vs 4.1%) and bronchitis (3.7% vs 2.7%) than the non-Gulf comparison group.[16] United Kingdom Gulf War veterans also reported respiratory medical complaints more commonly than medical personnel in the Era cohort, namely hay fever, sinus disorder, asthma and bronchitis.[21] US Gulf War veterans reported a significantly higher prevalence of sinusitis, bronchitis and other lung conditions, but similar rates of asthma.[20]

Some indication of the nature of respiratory conditions in Gulf War veterans is also gained through the findings of the outcomes of the clinical evaluation programs, although these do not include a comparison group. Respiratory symptoms were reported by 24/1000 (2.4%) of the first 1000 and 2.3% of the second 1000 British Gulf War veterans evaluated through the British Medical Assessment Program (MAP).[184] “Diseases of the respiratory system” were diagnosed in 16% of the first 1000 and 6% of the second 1000 British Gulf War veterans evaluated through the MAP,[183, 184] although no further information is provided on specific disorders within this ICD-10 coding category. Of the 62 Gulf War veterans in the second 1000 who had a “Diseases of the respiratory system”, this was a main condition in only 3 and an incidental condition in 59 Gulf War veterans.[183] "Diseases of the respiratory system" were diagnosed in 6.8% of 20,000 veterans evaluated through the US Department of Defense’s Comprehensive Clinical Evaluation Program[19] and in 10.5% of veterans in the combined US DVA Persian Gulf Veterans' Health Registry and CCEP data from 1993-1997.[182]

The lungs are part of the body's defence mechanism; and are vulnerable to absorption of a range of particulate, chemical or biological matter. Inhaled substances may gain access to the blood and body systems through the alveolar capillary membrane of the lungs, or may cause

local short or long term damaging effects to the lung tissue itself.[113] The nature or properties of the particle, such as the fibrogenicity of sand,[220] and the environment are important in determining the deposition of airborne particulate matter.[113] Natural and immune defence mechanisms such as alveolar macrophages and the mononuclear phagocytic system are activated in response to deposition of particulate matter.[220] Desert lung syndrome, a benign non-progressive pneumoconiosis only occurs after years of exposure to sand in the desert environment. Weathered silica, as is found in the Gulf Region, appears to be much less biologically aggressive than freshly fractured dust.[75] Fine sand and organic materials such as pigeon droppings have been associated with a respiratory condition 'Al Eskan Disease' condition reported among hospital personnel stationed in Saudi Arabia at the time of the Gulf War.[71, 220] Inhalation of particulate matter may have aggravated asthmatic conditions.[75] No cases of silicosis have been identified within the Gulf War veterans.[75] Exposure estimates suggest that Gulf War veterans were not exposed to sufficient silica to cause silicosis or other long term adverse health effects.[72]

The long term health effect of short term exposures to SMOIL are not known. The fire fighters who went to Kuwait had 10 years of experience fighting similar fires. They apparently did not use respiratory protective equipment, did not show the symptoms reported by the veterans and have not shown any long-term health effects.[17] In civilian fire fighters, cigarette smoking has been shown to be a major contributor to airways obstruction; and in non-smoking fire fighters, disease of the small airways was present only in fire fighters with at least 25 years of fire fighting.[221]

Some studies have investigated the relationship between respiratory symptoms and exposure to SMOIL. A US Department of Defense study of the self-reported symptoms of three groups of US Marines (n=2668), showed an association between prevalence of respiratory symptoms and proximity to the oil fires. Smokers reported more symptoms than non-smokers.[81] A second questionnaire study of 1599 US Army troops, showed that symptoms reported by Gulf War veterans, specifically eye and upper respiratory tract irritation, shortness of breath, cough, rashes and fatigue could be explained as a consequence of the exposure to SMOIL. The symptoms, particularly cough, correlated with recalled distance from an oil fire, and their incidence generally decreased after the soldiers left the Gulf. The investigators suggested that recall bias was a possibility with those who perceived certain environmental exposures as a problem during the deployment, including oil-fire smoke, pollution, heat exhaustion, flying insects, and sunburn also reporting deployment-associated respiratory symptoms at a significantly higher rate.[36] The relative risk for exposure to SMOIL was 1.6 (0.25-10.1) for ill veterans versus healthy veterans, although this difference was not statistically significant.[29]

Other studies have found no association between SMOIL exposure and increased ill-health. About half of the Danish Gulf War veterans reported exposure to SMOIL, but there was little difference in prevalence of exposure reporting between symptomatic and asymptomatic veterans.[32] Kroenke *et al* [33] also found no association between excess symptoms and SMOIL exposure.[33] A study of 125 UK soldiers compared spirometry results pre and post deployment and showed no significant difference, or association with degree of exposure to smoke from oil wells.[30]

An assessment of the toxicity of the contaminants of the oil fires and the magnitude and extent of the human exposures was undertaken by the RAND Corporation.[81] A health risk assessment using this information was carried out by the US Army Environmental Health Agency (USAEHA) soon after the Gulf War. The report was later extended providing more

detail on, for example, the troop movements. The risk assessments concluded that excess cancer risk was within the EPA guidelines for acceptability, and the risks of potential adverse health effects among the US troops exposed to smoke from oil fires.[75] The long-term effects of dermal exposure and inhalation of oil droplets, which occurred occasionally when troops were showered with unburnt oil, is being further investigated.[75]

The only cross-sectional study to undertake respiratory function tests was the Danish Gulf War Veterans' Study.[162] There were no significant differences in lung function between the Gulf War veterans and non-Gulf comparison group for FVC, FEV_1 or Peak Flow.[162]

Chronic cough, shortness of breath on exertion and sleep disturbances were some of the nonspecific symptoms reported by US Gulf War veterans. An observation that all five Gulf War veterans, referred from the US Veterans' Affairs Persian Gulf Registry for further respiratory assessment, had evidence of variable extrathoracic airflow obstruction led Das *et al*[165] to conduct a case control study of a convenience sample of the Persian Gulf Registry. Variable extrathoracic airflow obstruction has been observed in burns patients suspected of having thermal or smoke-related injury to their upper airways, but also has a number of causes including extrathoracic lesions including vocal cord paralysis, goitre and neoplasm. Extrathoracic airflow obstruction reduces inspiratory and expiratory flow; and is called variable when inspiratory flow is limited more than the corresponding expiratory flow.

In the case control study by Das et al[165] 37 Gulf War veterans and 38 control subjects completed a brief history of smoking and respiratory symptoms. Measurements of respiratory function included spirometry, fibreoptic bronchoscopy of subjects with physiological abnormalities who consented, and tracheal biopsy.of Gulf War veterans. A mid-vital capacity ratio of >1 (ratio of forced mid-expiratory to maximum forced mid-inspiratory flow >1) was used as the criterion standard for the diagnosis of variable extrathoracic airflow obstruction.

The mean FVC and the FEV_1/FVC ratio were not significantly different among the cases and controls, but there was a characteristic "flattening" of the inspiratory portion in many of the Gulf War veteran's flow-volume loops. Mid-vital capacity ratio was >1.0 in 32/37 Gulf War veterans compared with only 11/38 control subjects. The mean (SD) mid-vital capacity ratio of 1.37 (0.4) among Gulf War veterans was statistically significantly higher than the mean mid-vital capacity ratio 0.88 (0.3) among control subjects. Bronchoscopy showed inflamed larynx and trachea in all 17 of the Gulf War veterans who underwent tracheal biopsy. Chronic inflammation of the trachea was evident in all 12 who had an adequate biopsy taken. Smoking or allergy was not considered to be an adequate explanation for this finding, and it was proposed that a prolonged inflammatory process involving the upper airways might be a consequence of exposure to irritant fumes and gases from the Kuwaiti oil fires. The observation that upper airways rather than smaller airways were predominantly affected was also considered to be consistent with smoke inhalation. Limitations of this study included the convenience sampling and possible biases in the selection of cases and controls, uncontrolled histological and anatomical findings because bronchoscopy was only performed on consenting subjects with physiological abnormalities, and tracheal biopsies were only taken from Gulf War veterans. Although 86.5% of the 37 US Gulf War veterans had findings of extrathoracic airflow obstruction, the prevalence of this in the whole Gulf War veteran population has not been determined and the significance of this finding remains uncertain.[165]

In summary, respiratory tract complaints were a common, although generally non-debilitating, source of morbidity during the Gulf War. Respiratory symptoms and respiratory medical conditions have been significantly more commonly reported by Gulf War veterans in

cross-sectional studies conducted since the Gulf War, and 'diseases of the respiratory system' have been a common diagnosis in registry participants. Clinical evaluation of the association between self-reported exposures such as SMOIL and respiratory conditions is limited to only one study. This study suggested that there was evidence of chronic inflammation of the upper respiratory tract and variable extrathoracic airflow obstruction in Gulf War veterans, although the significance of this is not clear. There is very limited objective evaluation of respiratory function using measures such as spirometry, in the cross-sectional studies, using representative populations.

4.9 Infectious diseases

In anticipation of infectious disease cases, the US Navy, at the beginning of Operation Desert Shield, established a continuous epidemiological disease surveillance program and a laboratory for the diagnosis of infectious diseases in Saudi Arabia. Outpatient morbidity and hospitalisation data were collected from a population of approximately 40,000 US troops stationed in northeastern Saudi Arabia. The "disease non-battle injury" rate, which by definition included infectious diseases, was lower in this military campaign than in any other major war involvement of the USA; and the incidence of non-battle injuries decreased over time.[150] The extensive preventive preparations, comprehensive medical infrastructure and relatively favourable environmental conditions, such as isolation of most combat troops to barren desert locations during the cooler winter months, helped to minimise the impact of infectious diseases on the health and fighting capacity of personnel. The impact of infectious diseases that were commonly experienced during World War II desert campaigns such as shigellosis, malaria, sand fly fever and cutaneous leishmaniasis was less than anticipated. Mild cases of acute respiratory tract or diarrhoeal disease were the major causes of reported morbidity during the Gulf War.

The risk of acquiring many infectious pathogens is increased by travel to areas such as the Gulf, and multiple infectious diseases have been considered as a possible explanation for symptoms in Gulf War veterans. Many gastrointestinal, respiratory and cutaneous aetiologies have been considered, however, despite intense study, there has been no conclusive evidence to implicate any specific infectious agent.[40, 88]

The infectious disease hypotheses that have received most attention in Gulf War veteran studies include those involving leishmaniasis and mycoplasma. With respect to leishmaniasis, *Leishmania tropica* (*L. tropica)* is endemic in the Gulf region and is usually associated with cutaneous manifestations. However, only 19 cases of cutaneous leishmaniasis have been diagnosed in US Gulf War veterans.[17] An unexpected outcome among the US troops was a finding of visceral leishmaniasis due to *Leishmania tropica* that presented without the classic severe symptoms and signs of kala-azar.[150] This newly recognised systemic syndrome, which is now referred to as viscerotropic leishmaniasis, has been diagnosed in 12 US Gulf War veterans who had been stationed in the Gulf.[17, 222] All cases were reported within two years of returning from the Gulf. The most prominent findings in those affected included fever, hepatosplenomegaly, lymphadenopathy, mild anaemia, and elevated transaminases indicating liver damage, and all but one patient had objective signs of infection that would have been readily apparent on examination.[222] Despite the potential for ongoing harbouring of leishmania parasites, it is unlikely that undetected leishmania infection is the underlying cause for chronic non-specific health complaints in other veterans. Additionally, serological surveys have not suggested that leishmania plays a role in illnesses in Gulf War veterans generally, although it is not possible to screen specifically for visceral *L. tropica* infection via serology.

Some data exists regarding a potential association between mycoplasma infection, specifically *Mycoplasma fermentans* (*M. fermentans*) with both chronic fatigue syndrome and other illnesses in Gulf War veterans. It has been reported by Nicholson *et al*[223] that "altered" *M. fermentans* DNA sequences have been found in white blood cells of some Gulf War veterans.[167] The technique used to identify these mycoplasma gene sequences involved a gene hybridisation procedure using mycoplasma-specific gene probes (known as gene tracking). Bacterial DNA was found in the nucleoprotein complex (NPC) fractions obtained from white blood cells, and was identified even when polymerase chain reaction (PCR) had been negative. The investigators who described this technique reported that symptoms had also developed in family members of some veterans, which they believe gave further credence to their claim that illness is likely to be due to a biological and transmittable agent. They reported that 14/30 patients found to be positive for mycoplasma were subsequently treated with multiple cycles of antibiotics, and that 11/14 recovered. They also reported that, of 73 veterans with chronic fatigue-like symptoms treated with doxycycline, 55 had self-reported improvement or recovery.[224]

Evidence contrary to these findings has also been published. Firstly, some investigators have been unable to replicate the above findings, and have questioned the unstandardised and non-peer reviewed molecular techniques used.[40] Secondly, the reports by Nicholson *et al*[167] suggesting improvement following doxycycline therapy involved a self-referred group of patients without a comparable control group. In addition, two serological studies have not shown an association between mycoplasma infection and Gulf War related illness. The first of these was a matched case control study examining the prevalence of *M. fermentans* specific antibodies, measured by enzyme linked immunosorbent assay (ELISA) or Western Blot, before and after operation, and seroconversion rates in veterans with and without Gulf War related illness.[225] The results showed that, before deployment, 34/718 (4.8%) cases and 116/2233 controls (5.2%) had mycoplasma antibodies, and that there was no difference in seroconversion rates between cases and controls {8 cases (1.1%) vs 26 controls (1.2%)}. The second study, a serological survey by Gray *et al*,[104] showed no association between *M. fermentans* and deployment to the Gulf or postwar symptoms.

Because of the conflicting evidence, two further studies have been undertaken but are currently unpublished. The first of these is investigating whether diagnostic tests for Mycoplasma using PCR can identify Gulf War veterans with chronic unexplained illnesses.[88] The second study is investigating whether the effects on functional status and symptoms of administration of doxycycline or placebo over a one-year period to almost 500 veterans positive for Mycoplasma species by PCR[88, 166]

Another hypothesis involving a possible infectious aetiology for Gulf War illness is "systemic coccal disease".[226, 227] In brief, a non-culturable chronic systemic Gram positive coccal infection has been identified in some veterans by finding shells of dead cocci in specially evaluated samples of urine sediment. A study involving administration of multiple high-dose antibiotics to symptomatic veterans with cocci in urine samples is underway.[88]

Other infectious diseases known to be endemic to the Gulf which have been considered but dismissed because of a lack of documented cases include Q fever, brucellosis, rickettsial infections (typhus or spotted fever), arboviruses (Sandfly fever, dengue, Rift Valley, Congo-Crimean, West Nile), hepatitis A and E, other viruses such as enteroviruses and retroviruses, malaria, sexually transmitted diseases, schistosomiasis, echinococcus and tuberculosis.[150, 166] Fungal skin infections, acute diarrhoeal diseases (especially *E.coli* and shigella), and acute respiratory infections were the most common infections reported in ground troops, but these

infections do not have the potential for chronic sequelae and therefore have also been discounted.

Other evidence against an infectious process has been suggested by the fact that large epidemiological studies of Gulf War veterans have not shown increased rates of hospitalisation or mortality from infectious diseases.[166] Researchers have concluded that it is unlikely an infectious process could cause significant long term health problems and remain undetected, particularly as no consistent pattern of objective signs or laboratory abnormalities to indicate an infectious process have been found.[88, 150]

4.10 Immunisations

Previously published findings on the health of Gulf War veterans has suggested a potential link between adverse health outcomes and receipt of multiple vaccinations.[28, 60, 61] The underlying hypothesis for such a link is based on the fact that vaccination induces an immune response that may, under some circumstances, result in chronic stimulation of the immune system and a shift in the T cell cytokine profile from a Th1 to a Th2 response.[228] This in turn may be associated with the development of autoimmune disorders, secondary blood dyscrasias/neoplasms, or chronic fatigue syndrome. Four aspects of the Gulf War vaccination program were thought to be particularly relevant, namely that pertussis was used as an adjuvant for UK (but not US or Australian) personnel, multiple vaccinations were given simultaneously, many vaccines were given after personnel were deployed; and finally, there may have been an interaction between the vaccine regimen and pesticide use.[61, 228]

The largest study to address this issue was performed in the UK.[21, 61] Unwin *et al*[21] found that the receipt of vaccines against agents of biological warfare (plague and anthrax with pertussis adjuvant) was associated with a slightly increased risk of a multisymptom illness in the Gulf War cohort (OR 1.4; 95% CI 1.1-1.9), but those who received routine vaccinations were generally not at increased risk. Pertussis vaccine was weakly associated with an increased risk of the multisymptom illness in Gulf War veterans who had their vaccination records (OR 1.3; 95% CI 1.0-1.7). In addition, Gulf War servicemen who received seven or more vaccines were found to have a slightly increased risk of reporting the multisymptom illness (OR 1.9; 95% CI 1.3-2.8) but Bosnia veterans were not, even though they had also received multiple vaccines. The receipt of multiple vaccines was associated with poorer health for other main health outcomes under study, after controlling for deployment, but the interaction (ie, differences in the effect of one or more variables according to the values of one or more other variables[202]) between deployment and multiple vaccinations was only significant for health perception and physical health. No associations with traditional military stressors, pesticide use or vaccines were found. Further analysis showed that the association between administration of individual biological vaccines and illness may have been attributable to a biased recollection of vaccine side effects and later illness, with veterans who recalled experiencing vaccine side effects more likely to have current symptoms (GW cohort OR 2.8; 95% CI 2.4-3.3 and Bosnia cohort 2.2; 1.6-3.1), however the relationship between current symptoms and receipt of multiple vaccines remained.

Further analyses by Hotopf *et al* [61] examined the association between self-reported symptoms and receipt of multiple vaccines (≥5) either before or during deployment. Receipt of multiple vaccines before deployment was associated with posttraumatic stress reaction only, but receipt of multiple vaccines during deployment was associated with five other health outcome measures, namely multisymptom illness, fatigue, poorer response on the General Health Questionnaire, poorer health perception and poorer physical functioning.

Those who were vaccinated during deployment were more likely to have received vaccines against agents of biological warfare. Traditional combat stressors did not modify the effects of multiple vaccines, and there was no interaction between multiple vaccines and self-reported pesticide use. A marginally significant association was found between vaccination after deployment and asthma (p=0.06), but no association was found between vaccination before deployment and atopic conditions. The investigators concluded that administration of multiple vaccines per se may not be harmful, but may be associated with adverse health outcomes when given in conjunction with the stress of deployment.[61]

There were several limitations of the Hotopf *et al*[61] study. Firstly, the analysis was based on those Gulf War veterans with vaccine records, however, only 923 (28 %) of the 3284 (70.4%) Gulf War veterans who responded to the original study reported that they had vaccine records. Secondly, inadequacies in data quality in relation to both record keeping in the Department of Defence medical records system before and during deployment, and in the numbers and types of vaccines self reported by veterans made it difficult to draw firm conclusions from this study.[56] Hotopf *et al*[60] reanalysed the data in response to criticisms that the methodology did not take into account a comparison of the exposures to multiple vaccines before and during deployment and found similar results. The investigators confirmed their previous conclusions, but acknowledged that their findings were preliminary and needed to be replicated.

An early clinical and laboratory study (before the Gulf War) designed specifically to look for adverse effects from repeated intensive parenteral inoculation with a variety of vaccines found no significant adverse health outcomes.[229] In addition, despite the fact that some Canadian veterans were immunised along with British soldiers according to the UK protocol and other Canadian personnel received vaccines according to a different protocol, no difference has been found in the prevalence of post-deployment health complaints between the Canadian groups.[22] Cherry *et al*[28] found that about a quarter of Gulf War veterans had vaccination records. Those who had records tended to report more vaccinations than those who did not. The timing of vaccinations (before leaving or after arrival) had no effect on health indices, but the number of vaccinations was associated with higher scores on a factor analysis based "peripheral" factor that was weighted on symptoms associated with skin and musculoskeletal complaints.[28] Finally, other researchers have concluded that there is no precedent for non-live vaccines or adjuvants to cause prolonged health problems without demonstrable pathology.[88, 166]

4.11 Chronic fatigue and immunological markers

Symptoms of fatigue, tiredness, lacking in energy, needing to rest more or feeling unusually sleepy/drowsy have been reported by up to 50% of Gulf War veterans in several studies[20, 21, 160] and more frequently than by the non-Gulf comparison groups. A US study found that extreme fatigue every day, or almost every day, was reported by 23% of Gulf War veterans and 9% of non-Gulf veterans.[160] Fatigue lasting 24 hours was reported by 20% of Gulf War veterans.[20] In a UK study, feelings of tiredness were the most troublesome symptoms, with the highest mean symptom scores in both the Gulf War veteran and comparison groups, although as with all other symptoms the score was higher in the Gulf War veteran group.[157] Being "overly tired/lack of energy" was reported by 22.2% of a New England cohort of Gulf War veterans, but by 78.2% of a high symptom group and by 30.7% of a moderate symptom group within this cohort.[159]

The prevalence of neuropsychological symptoms, including symptoms related to fatigue and sleeping difficulties which had their onset during or after the period of the Gulf War, was significantly higher in Danish Gulf War veterans than the comparison group, but no significant differences were found for such symptoms that had their onset before the period of the Gulf War.[162]

Chronic fatigue syndrome or myalgic encephalitis was self-reported as a medical condition by 3.3% of UK Gulf War veterans.[21] Gulf War veterans were more likely than the Bosnia and Era cohorts to have substantial fatigue (OR 2.2; 95% CI 1.9-2.6 and OR 3.6; 95% CI 3.2-4.2 respectively) according to their scores on the Chalder fatigue scale.[21, 230] UK Gulf War veterans who believed they had Gulf War syndrome were more fatigued, more distressed, more likely to have a posttraumatic stress reaction and to fulfil the criteria for a multisymptom illness.[156] Between 1.0-2.9% of Gulf War veterans reported symptoms consistent with chronic fatigue as a medical condition, and the differences between the Gulf War and comparison groups were more marked in defence personnel in the National Guard/Reserve rather than in the regular military.[16] All the criteria for chronic fatigue syndrome were met by 8 subjects in a study of 1155 Gulf War veterans and 2520 non-deployed personnel that investigated the prevalence of a chronic multisymptom illness, for which chronic fatigue was a key feature. Of these, seven also were classified as severe cases and one as a mild-moderate case of this chronic multisymptom illness.[73]

Although fatigue as a symptom and as a medical condition has been reported to be more common among Gulf War veterans than non-Gulf veterans, comprehensive evaluation of fatigue or chronic fatigue has been limited.

Although the cause of chronic fatigue syndrome remains unexplained, an association with a variety of immunological changes has been reported. The changes include a reduction in delayed-type hypersensitivity skin responses, impaired lymphocyte responses to mitogens, depressed Natural Killer (NK) cell cytotoxicity, decreased production of IFN-gamma and IL-2, increased expression of activation markers, and increased levels of autoantibodies to insoluble cellular antigens.[231] With this background, it has been hypothesised that chronic fatigue symptoms reported by veterans may be due to a shift in the T cell cytokine profile from a Th1 to a Th2 response.[228] Th1 cytokines include IL-2, IFN gamma, and TNF alpha which support cell mediated immunity (CMI), and Th2 cytokines include IL-4, IL-5, IL-6, and IL-10 which support humoral immune responses.

One stimulus that has been proposed as a potential instigator of this shift in cytokine production is administration of Th2-inducing vaccines, particularly those with a large antigen load (eg plague, anthrax, typhoid, tetanus and cholera) and/or those which used pertussis as an adjuvant. Another potential stimulus proposed is stress, as cortisol drives a Th2 response. Exposure to carbamate or organophosphate insecticides has also been suggested as a possible trigger, as these compounds inhibit IL-2 driven events required for Th1 function.[228]

A few studies have examined this in Gulf War veterans. One of these examined the peripheral blood T-cell cytokine production and the NK cell activity of Danish Gulf War veterans and found no difference between veterans and controls.[168] However, the investigators did not specify whether or not the veterans included in the study had somatic or psychological symptoms. Another study examined T cells, B cells, NK cells and cytokines in individuals with chronic fatigue syndrome (in both Gulf War veteran and comparison groups) and in healthy Gulf War or non-Gulf War veteran controls.[169] The results showed no significant difference for immune variables amongst non-Gulf War veterans regardless of whether or not they had chronic fatigue syndrome. Amongst Gulf War veterans, individuals

with chronic fatigue syndrome had significantly more total T cells (CD3+), more MHC class II T cells (CD3+, CD4+), and a lower percentage of NK cells than Gulf War controls. However, even in this group, the cell surface marker data was still in the normal range. The symptomatic Gulf War veterans also had significantly higher levels of IL-2, IL-10, IFN gamma and TNF alpha than controls, suggestive of a trend towards up-regulation of the type 1 cytokine response, but with no observed shift from a type 1 to a type II response. The authors concluded that there was no evidence of immune dysfunction in sporadic chronic fatigue syndrome, but that Gulf War veterans with severe fatiguing illness did have an altered immune function, even though their results were still within the normal range.

4.12 Neurological symptoms

Neurological symptoms have been more commonly reported by US Gulf War veterans than non-Gulf comparison groups. These include headaches, concentration difficulties, numbness or tingling in feet and arms, blurred vision, tremors/shaking and difficulty with speech.[20]

"Symptoms of cognitive dysfunction" have also been significantly more commonly reported among US Gulf War veterans compared with non-Gulf War military personnel (18.7% vs 7.6%).[16] This was shown to be associated with exposure to solvents/petrochemicals, smoke combustion products, sources of lead from fuels, pesticides, ionising/nonionising radiation, chemical warfare agents, pyridostigmine bromide use, sources of infectious agents and physical trauma.

US and UK Gulf War veterans have also reported neurological symptoms and conditions more commonly than non-Gulf comparison groups in several studies, including migraines,[20, 21] repeated seizures, recurrent headaches and neuralgia or neuritis.[20]

UK Gulf War veterans have been more likely, than non-Gulf veterans, to report symptoms suggestive of peripheral neuropathy (12.5% vs 6.8%) and widespread pain (12.2% vs 6.5%).[157] Areas shaded by participants on manikins in a postal questionnaire, to indicate numbness or tingling that had been troublesome in the past month were used to define patterns considered to be consistent with toxic neuropathy. Participants were asked to shade a second manikin to indicate sites of pain that had been troublesome in the past month. Possible neuropathy was considered "limited" if numbness or tingling was restricted to one or both feet and "extended" if it was reported in both feet and at least one hand or lower leg. Symptoms considered suggestive of peripheral neuropathy were more commonly reported by Gulf War veterans (6.0% vs 4.5% for "limited symptoms" and 8.5% vs 2.3% for extended symptoms) than the non-Gulf cohort.[157]

Using factor analysis, Cherry *et al*[157] identified a factor that included predominantly neurological and neuropsychological symptoms. Symptoms loading onto the "neurological" factor included 'problems doing up buttons on your chest', 'difficulty in standing up from a chair', 'fainting', 'feeling too weak to complete what you are doing', 'losing you balance', 'painful tingling in your hands or feet', 'loss of sensation in your hands or feet', 'difficulty in lifting down an object from just above your head', 'double vision', 'shortness of breath when walking with other people your own age', 'feeling unsteady in walking', 'feeling dizzy', and 'tingling under your skin'. Thus, this factor had a high weighting on symptoms that might have arisen from poor functioning of the central nervous system, as well as peripheral symptoms. The scores on the "neurological" factor, however, were no different between the Gulf and non-Gulf cohorts.[28]

Danish Gulf War veterans more commonly reported neuropsychological symptoms that had occurred during the preceding 12 months than the non-Gulf comparison group.[163] These included concentration or memory problems, repeated fits of headache, balance disturbances or fits of dizziness, abnormal fatigue not caused by physical activity and problems sleeping all night. Significantly more Gulf War veterans reported at least one (61% vs 35%) and three to five (21.4% vs 6.2%) of these neuropsychological symptoms. Psychosocial and physico-chemical factors were strongly associated with neuropsychological symptoms.[163]

The associations between exposures during the Gulf War and adverse neurological outcomes, as well as more general measures of health were considered in a number of studies. A survey of 2005 randomly selected US veterans suggested that some veterans experienced symptoms during the Gulf War that indicated overexposure to pesticides. Symptoms were most likely to be severe for veterans who applied organophosphate pesticides, but the majority of symptoms were mild, localised and short term reactions.[94] Surveys of US and Danish veterans found that those with and without neurological symptoms reported similar prevalence of pesticide exposures.[32, 33] Exposure to repellents was not associated with significant health outcomes in a US study.[19] However, another study reported that the number of days handling pesticides was related to a "neurological" factor score and to symptoms of peripheral neuropathy.[28] In a study of UK veterans, multiple chemical sensitivity was strongly associated with exposure to personal pesticides (OR 10.9; 2.6-45.8) and with pesticides on clothing (OR 12.3; 5.1-30.0).[148] UK troops had a relative risk (RR) of 5.6 for exposure to pesticides and 5.5 for exposure to repellents for ill veterans vs healthy veterans.[29] Use of flea collars was associated with impaired cognition (RR 8.7; 3-25).[31]

Haley *et al*'s primary study in relation to Gulf War veterans health[158] is summarised in Table 4.1. Haley *et al*[158] found that at least 25% of ill veterans amongst those surveyed had symptoms that may have represented generalised neurological injuries. On the basis of this finding, Haley *et al* hypothesised that small subsets of veterans with discrete syndromes, or variants of a single syndrome, due to neurotoxic exposures experienced during the Gulf War, were hidden amongst the larger numbers of veterans with other medical or psychological illnesses.[158] The above study had a number of limitations. The low participation rate (41%) suggests that selection bias may have affected the results, and the sample size was small. Participants were older, were more likely to report a serious illness since the war, and were more likely to be unemployed than non-participants. Biases may have resulted from the non-random selection of the overall study group, as the reserve construction battalion which Haley *et al* studied was known to have a high prevalence of post-war illness. The reserve battalion was not representative of Gulf War veterans generally as the study group was older than other deployed forces, was often employed in other full-time non-military careers with other occupational exposures and risks that may have confounded the results, and had been exposed to numerous medical examinations and media contacts before the survey was conducted.[25] Although this survey included both ill and non-ill Gulf War veterans, it did not include a comparison with a non-deployed military control group.

Haley and Kurt[31] hypothesised that the symptomatology reported by Gulf War veterans was explained by variants of organophosphate induced delayed polyneuropathy (OPIDP) that could result in chronic neurological impairment. Haley and Kurt investigated the associations of three factor analysis-derived syndromes and risk factors of self-reported exposures to neurotoxic chemicals and chemical interactions that inhibit butyrylcholinesterase and neuropathy target esterase. The risk of Factor 1 "impaired cognition" was significantly greater in veterans who reported wearing flea collars during the war than those who never wore them. Whilst 95% of veterans in this survey reported having

taken PB during the war, the effect was not modified by the number of PB tablets taken or side effects experienced. Factor 2 "confusion-ataxia" was eight times more common in veterans who reported having experienced a likely chemical weapons attack, and was increased in veterans who had been in a far northeastern sector of Saudi Arabia on the fourth day of the air war (a sector allegedly exposed to chemical warfare agents). Factor 2 did not increase with number of PB tablets taken, but it did increase with the recall of certain "advanced adverse effects" from taking pyridostigmine bromide. Effects of self-reported perceived chemical weapons exposure and certain "advanced adverse effects" from PB were associated. Factor 3 "arthro-myo-neuropathy" increased with the frequency and amount of government issued insect repellent containing 75% DEET (N,N-diethyl-m-toluamide) in ethanol applied to their skin and with advanced adverse effects from PB. The small numbers involved did not allow for the assessment of synergism between the effects of repellent use and adverse effects attributed to PB. These three outcome factors were associated with risk factors for organophosphate exposure, but were not significantly associated with the thirteen other risk factors, such as multiple immunisation, combat stress or smoke from oil well fires, that had been considered in other studies as suspected causes of Gulf War illnesses.

Haley and Kurt concluded that the generally mild neurological impairment they observed in Gulf War veterans[31] suggests that the three outcome factors may represent variants of OPIDP due to varying exposures to organophosphate nerve agents potentiated by interactions with other chemical exposures such as PB, other organophosphates in the pesticide preparations used, the older age of veterans, and different "brain reserve capacity" at the time of the Gulf War. A major limitation of this study, and the conclusions drawn from it, is the lack of symptom and exposure data on a comparison group, either of non-deployed veterans or veterans deployed in other active deployments.

Haley *et al*[170] also evaluated neurological function, through a nested case control study[202] of 23 veterans with the three strong factor analysis-derived syndromes and 20 controls from the same battalion (10 deployed and 10 non-deployed), using neuropsychological tests, audiovestibular function, somatosensory evoked potentials, brain stem auditory evoked potentials, visual evoked potentials, MRI and SPECT scans. There was also follow up sensory and peripheral nerve testing for five cases, blood tests, independent neurological examination by a neurologist and review of each subjects findings by six neurologists. The study found impairment in cases on the two global measures of brain dysfunction, the Halstead Impairment Index (P=.01) and the General Neuropsychological Deficit Scale (P=.03). Scores for factor 2 and 3 cases exceeded normal limits. The mean scores for cases were of borderline significance when compared to controls for factor 1 and 3, but were significantly greater (more abnormal) for factor 2 cases. Approximately two-thirds of the subjects had at least one neurological abnormality on physical examination, and most commonly this was related to reduced strength of the lower extremities. There were no significant differences in the frequency of neurological findings on examination, or MRI or SPECT scans, between cases and controls. Independent review of the findings of each subject individually by the examining neurologists and the study investigators found the clinical and laboratory investigations to be non-specific and not sufficient to diagnose any known neurological syndrome in any subgroup of the subjects. Two of the cases were discovered to have intercurrent medical conditions that could cause neurological dysfunction.[170]

This study[170] has been criticised on a number of levels. There was no adequate control group, there was a reliance on self reported exposure with possible recall bias because the participants were self selected, and there was a lack of clinical validity for measures of

neurological damage. The lack of significant differences between cases and controls on neurological examination and the non-specific nature of the findings on a battery of tests did not support a conclusion of neurological damage. As a result of the study design, the cases may have represented more chronic severely ill individuals than if they were incident cases, the sample sizes were small.[25]

Haley *et al*[232] also assessed functioning neuronal mass in twelve veterans with factor 2 "confusion-ataxia" and 15 controls (eight Gulf War veterans who remained well and seven who did not serve in the Gulf War and also were well) in both basal ganglia by measuring the ratio of N-acetyl-aspartate to creatinine with proton magnetic resonance spectroscopy and central dopamine activity by measuring the ratio of plasma homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MPHG).[232] The authors concluded that the functioning neuronal mass in the left basal ganglia had affected central dopamine production in a lateralised pattern, and, given the strong association, previous findings of animal studies of unilateral striatum ablation studies and the standardisation of conditions in their study, that the effect is likely to represent a real physiological effect. They also concluded that these findings supported their theory that Gulf War illnesses are a neurological illness, in part due to injury to dopaminergic neurons in the basal ganglia, and do not support the theories that Gulf War illnesses result from posttraumatic psychological stress.[232]

It has been proposed that DEET may accelerate the absorption of other compounds and that absorption of DEET would increase when skin is hot (as in the desert) and occluded eg under protective clothing.[31] The synergistic effects of combinations of the cholinesterase inhibitors has been the subject of animal studies,[122-124, 126] but the applicability of the results to humans is uncertain. It has been hypothesised that genetic polymorphism of enzymes such as paraoxonase/arylesterase 1 (PON1) and butyrylcholinesterase (BuChE) may have increased the susceptibility of Gulf War veterans to risk of effects from exposure of Gulf War veterans to neurotoxic chemicals that require these enzymes for detoxification.[117, 118] Synergistic effects of combinations of exposures may have played a role, but the findings and their significance in humans in relation to this are inconclusive.[25]

It has been reported that French troops did not experience "Gulf War syndrome" and that possible reasons for this were because they were not exposed to chemical warfare agents, did not use OPs and took PB on a very restricted basis.[121] Bell *et al*[29] provide some data suggestive of association between exposure to pesticides or insect repellents or paints and increased symptoms. They found non-significant associations with chemical warfare agents and PB, but the numbers of veterans surveyed was small (n=41).

Although the results have not yet been published in the scientific peer reviewed literature, a recent study in the US has been reported as finding that, of 700 000 Gulf War veterans, 40 had motor neurone disease (known in the United States as amyotrophic lateral sclerosis or Lou Gehrig's disease). This case rate of 6.7 per million was contrasted with a case rate of 3.5 per million for the 67, of 1.8 million US Defence personnel in the same period who did not deploy to the Gulf War, who had motor neurone disease[233] (http://www.gulflink.osd.mil/news/na als remarks 10 dec01.html).

4.13 Musculoskeletal

During the Gulf War, musculoskeletal injuries occurred in over half (57%) of the 222 active duty soldiers referred to five US Army Medical Centres for medical attention.[234]

Musculoskeletal symptoms such as joint pain and stiffness, joint swelling, pain without swelling or redness in several joints, muscle pain, back aches or pain and neck aches or stiffness were commonly self-reported by Gulf War veterans and less commonly by the comparison groups in several cross-sectional studies.[20, 21, 38, 73, 162] Joint pain was reported by 31.5-45% of participants,[20, 21, 38, 73] joint stiffness by 30-40%[21, 73] and back ache or back pain by 27.9-44% of participants.[20, 38]

A variety of musculoskeletal medical conditions such as back disorder, arthritis or rheumatism, lumbago, diseases of muscles and symptoms of fibromyalgia were more commonly self-reported by Gulf War veterans than by non-Gulf comparison groups.[16, 20, 21] Diseases of the musculoskeletal system accounted for 6.1-21.2% of the diagnoses in an analysis of US federal and civilian hospitalisations, but there was no indication that Gulf War veterans were suffering increased proportional morbidity ratios for diseases of the musculoskeletal system when compared to other veterans. They did, however, experience proportionally more hospitalisations for specific diagnoses such as fractures of bone and soft tissue injuries.[187] Extensive clinical evaluation of twenty Gulf War veterans with severe subjective symptoms of muscle fatigue, weakness or myalgias found no objective evidence of a neuromuscular disorder.[235] The proposal that a Gulf War myalgia syndrome has been identified[114] has been disputed.[236]

Kroenke *et al*[33] found that joint pain was correlated (correlation coefficient $r > 0.35$) with muscle pain, and there was no association between joint pain as a symptom and 20 different self-reported Gulf War exposures. Joint pain was reported by a similar percentage of participants (46-53%) regardless of exposure, and this pattern was similar to that for other symptoms and the exposures. There did not appear to be a synergistic effect between pyridostigmine bromide and pesticide exposure in relation to the self-report of symptoms of joint or muscle pain or in relation to musculoskeletal diagnoses. This lack of a synergistic effect was consistent for all musculoskeletal symptoms under examination.[33]

Several studies have investigated associations between musculoskeletal symptoms and Gulf War exposures. The musculoskeletal body system symptom score was found to be associated with self-reported exposure to pesticides, debris from Scud missiles and chemical and biological warfare agents, but not with anti-nerve agent pills.[38] Among US Gulf War military personnel, fibromyalgia was significantly associated with an increased prevalence of exposure to solvents/petrochemicals, smoke/combustion products, sources of infectious agents, psychological stressors, sources of lead from fuels, pesticides, ionising/nonionising radiation, chemical warfare agents, pyridostigmine use, physical trauma and place of service within the Gulf War theatre.[16]

4.14 Skin

During the Gulf War, skin infections and infestations, and eczema and its variants were found to be the most common reasons for dermatological referral in a case series of dermatological referrals.[171, 172] The range of problems were similar to those encountered in dermatology practice or from previous war zone experiences although at least some of the differences were attributed to the particular environment and conditions of the Gulf. Eighteen closely related groups of diseases accounted for 78.3% of cases.[172] It has also been postulated that personnel suffering major skin problems were unlikely to have been sent on active duty to the Gulf,[171, 172, 237] unless they were more senior "essential" personnel.[237] However, in one series representing one third of cases the problem had been present for three months and in most cases had preceded Gulf War deployment.[171]

Factors that may have contributed to the development or exacerbation of skin conditions in the Gulf War include the desert climate with its heat, aridity and extremes of temperature, the occlusive effect of chemical protective clothing, the increased ultraviolet light exposure and photosensitivity; the irritating and chafing effects of sand, insect bites; adverse living conditions and stress. Dermal exposures to sand and soot may have produced reversible short-term symptoms such as rashes, skin irritation and scaling, and even scleroderma.[72] Pre-existing dermatoses such as acne, psoriasis or atopic conditions may have been aggravated, or in some instances improved, in the environment that the Gulf War was conducted in.[171, 172, 237] However, exposure modelling suggests that there are negligible health risks from dermal exposure during the Gulf War.[72]

Skin symptoms such as rash, itchy skin or dryness or scaliness of skin have been self-reported by 11.7-29% of Gulf War veterans and less commonly by non-Gulf comparison groups in several cross-sectional studies.[16, 20, 38, 73, 157, 162]

Skin-related medical conditions such as dermatitis, diseases of the hair or scalp, eczema or psoriasis were self-reported by 4.2-25.1% of Gulf War veterans in several cross-sectional studies; and, in a similar pattern to symptoms, were less commonly reported by comparison groups.[20, 21, 162] Skin conditions were among the 15 most frequently self-reported medical disorders in one study of UK Gulf War veterans with 21.3% of Gulf War veterans reporting dermatitis, 16.5% reporting diseases of the hair or scalp and 7.8% reporting eczema or psoriasis; all significantly more common than reports by the comparison groups.[21] Skin cancers were reported by between 0.8-1.1% of Iowa Gulf War veterans and by between 0.2-0.6% of the comparison subgroups.[16] Nine (0.05%) of the 20,000 participants of the US CCEP had skin cancers.[19]

Kroenke *et al*[33] found that there was no association between rash or hair loss as a symptom and 20 different self-reported exposures. Rash and hair loss was reported by a similar percentage of participants (28-32% and 12-16%) regardless of the type of exposure. There did not appear to be a synergistic effect between pyridostigmine bromide and pesticide exposure in relation to the self-report of symptoms of rash or hair loss or in relation to skin conditions as a diagnosis. The dermatological body system symptom score was not associated with self-reported exposure to pesticides, debris from Scuds and chemical or biological warfare agents.[38]

4.15 Gastrointestinal conditions

The Danish Gulf War Study considered risk factors for gastrointestinal health.[32] Compared with non-Gulf veterans, Danish Gulf War veterans had a significantly higher prevalence of self-reported gastrointestinal symptoms that were characterised by constant or occasional recurrent diarrhoea and frequent rumbling of the stomach within the preceding 12 months (9.1% vs 1.7%). After multivariate analysis, only two exposures, burning of waste or manure and exposure to insecticides against cockroaches, were significantly associated with gastrointestinal symptoms. Other associations with tooth brushing using water contaminated with chemicals or pesticides, and bathing in or drinking contaminated water, approached statistical significance. There appeared to be a relationship between the number of exposures and the gastrointestinal health outcome of recurrent diarrhoea and frequent rumbling of the stomach, with 74 subjects having a history of 3-4 exposures and a prevalence of 18.9%, 164 subjects having two exposures and a prevalence of 12.8%, and 270 subjects having one exposure and a prevalence of 7.4 %. One hundred and fifty-three subjects without any symptoms, had a prevalence of 2%, and this was comparable to that of controls (1.7%).[32]

4.16 DU related health problems

In 1993-1994, 33 veterans involved in "friendly fire" incidents which were thought to involve exposure to DU underwent medical evaluation at the Baltimore Veteran's Affairs Medical Center, USA. Mean urinary uranium concentration was found to be significantly higher in veterans with metal fragment retention (confirmed by X-ray) compared to those without metal fragments.[48] In 1997, 29 of these DU-exposed veterans and 38 non-exposed veterans were re-assessed through history and a medical examination.[49]

DU-exposed Gulf War veterans with retained metal fragments were excreting elevated levels of uranium in their urine seven years after the first exposure. The correlation between 1994 and 1997 urinary uranium results was highly statistically significant (R^2 =0.86). The correlation between spot uranium concentrations and 24-hr determinations was also extremely high (R^2 =0.98) and spot urine measurements were recommended for future monitoring. Adverse effects on the kidneys were not present. Nine veterans had uranium indices above the limit of detection for the whole-body counting measurements (all were DU-exposed veterans). Only one was higher than the USA recommended annual exposure allowance for the general public (0.1 rem/year). In one set of neurocognitive function tests, premorbid functioning was the best predictor of performance. In another set, functioning was significantly associated with urinary uranium concentration. A high serum prolactin level was also significantly associated with urinary uranium concentration.[49] Between 1998 and 1999, 169 Gulf War veterans submitted 24-hr urine samples and described their likely exposure to DU during the Gulf War. The results suggest that elevated urinary uranium and long term health effects as a result of DU exposure, eg as a result of the clean up of the tank fire at Doha, were unlikely in the absence of retained shrapnel.[50]

Over 60 veterans are being followed, as these veterans still have elevated uranium concentrations in their urine but the general health indicators were normal.[238] Thirty six US soldiers are known to have embedded shrapnel from friendly fire.[45] All their children, fathered since the Gulf War, are normal.[238]

4.17 Reproductive outcomes

In a cross-sectional study of 15,000 Gulf War veterans and 15,000 non-Gulf War veterans, Kang *et al*[239] compared self-reported reproductive health outcomes (spontaneous abortions, still births, pre-term delivery, birth defects and infant mortality) for an "index" pregnancy, ie the first pregnancy ending after June 30 1991 regardless of outcome. Female Gulf War veterans reported a higher rate of both miscarriages (adjusted OR 1.35; 0.97-1.89) and stillbirths (adjusted OR 1.26; 0.46-3.49) than the non-Gulf War comparison group, but neither difference was statistically significant. Male Gulf War veterans reported higher rates of both miscarriages (adjusted OR 1.62; 1.32-1.99) and stillbirths (adjusted OR 1.65; 0.91-2.98), but only the former rate was statistically significant. Both male and female Gulf War veterans reported statistically significantly higher rates of birth defects among live born infants (likely birth defects adjusted OR 1.94; 1.37-2.74 and OR 2.97; 1.47-5.99 respectively). When the comparison was limited to "moderate to severe" likely birth defects, the adjusted ORs were 1.78 (1.19-2.66) for males and 2.80 (1.26-6.25) for females. There were no statistically significant differences, by Gulf War deployment status, among men or women for the outcomes of stillbirths, pre-term deliveries or infant mortality. Whilst the authors concluded that the risk of veterans reporting birth defects among their children was associated with service in the Gulf War, they acknowledged the potential for reporting bias and recommended that these observations be confirmed by a review of medical records.[239]

In the cross-sectional study of Canadian Gulf War veterans, the rate of reported birth defects was within expectations for the general population with 103/3205 live births (3.2%) plus 38 stillbirths among Gulf War veterans and 46/3588 live births (1.3%) plus 44 stillbirths among the comparison group.[22]

Studies that retrospectively reviewed birth records found no excess of adverse reproductive outcomes among the births to Gulf War veterans following the Gulf War,[190, 240] even when births outside military hospitals and defects developing in the first year of life were included.[191] Adverse reproductive outcomes were similar to that expected in the general population,[240] although the small numbers of births and defects limited the statistical power for making comparisons.[240]

Cowan *et al*[190] compared 75,461 live births to 578,705 Gulf War veterans and 699,954 non-deployed veterans in 135 military hospitals in 1991, 1992, and 1993. The overall risk of any birth defect was 7.45%, and the risk of severe birth defects was 1.85% compared to a general population risk of 8.4% and 1.9% respectively. They found no evidence of reduced fertility, and no significant differences in the male:female birth ratio, the risk of 'any birth defect' or of 'severe birth defects' in children of male and female Gulf War veterans. There was no association between risk and either duration of service in the Gulf or the interval between return from the Gulf region and the child's date of birth.[190] This study included live births, but not other pregnancy outcomes such as terminations of pregnancy or stillbirths. A limitation of this study was the exclusion of children born after their mothers or fathers left active duty or children born to reserve-component personnel. In addition, births paid for by the military but occurring in civilian hospitals were included in the estimates of live births and fertility rates, but excluded from the estimation of the risk of birth defects because of data reliability concerns.

The prevalence of birth defects in live born infants in Hawaii, born during the prewar and postwar periods, was not significantly different for Gulf War veteran and non-deployed veterans, nor different in prewar and postwar conceptions of the Gulf War group. The rate of major congenital malformations in live born infants of Gulf War veterans (2.07/100 live births) in Hawaii between 1989 and 1993 was similar to that in the children born to the non-deployed veterans' group (2.15/100 live births), as determined by matching of birth records with a birth defect surveillance program. The small numbers of birth defects in each category limited additional comparisons and interpretation of the data.[191] A strength of this study was the inclusion of live births to parents who had left the military as well as births in civilian hospitals, and the inclusion of birth defects diagnosed during the first year of life.

4.18 Cancer

The cancer experience of Gulf War veterans has been investigated through studies of hospitalisations[19, 173] and mortality,[109, 192, 193] through the registry referral programs[19] (section 4.21) and to a limited extent through cross-sectional studies.[16, 20]

Gulf War veterans were at higher risk of hospitalisation for neoplasms during 1991, but not during 1992-3, and these were largely benign neoplasms, although the standardised risk ratio (SRR) for testicular cancer was slightly elevated during the last five months of 1991 (SRR 2.12; 1.11-4.02).[188] However, by four years after the end of deployment the cumulative probability of hospitalisation for testicular cancer was the same (0.034% for the Gulf War veterans and 0.035% for the non-deployed group. The risk factors were studied in more detail. The effect of age on the risk of testicular cancer was modest, but race was found to be an important predictor of hospitalisation for testicular cancer, with blacks and Hispanics at

greater risk relative to whites (RR 0.19; 95% CI 0.12-0.29 for blacks, and RR 0.59; 95% CI 0.39-0.91 for Hispanics, other and unknown, relative to whites). Risk also varied with occupation, (RR 1.56; 95% CI 1.23-2.00) for those in electronic equipment repair occupations, (RR 1.26; 95% CI 1.01-1.58) for those in electrical/mechanical repair occupations and (RR 1.42; 95% CI 0.93-2.17) for those in construction-related trades, compared with those in other occupations. Deployment status was not important (RR 1.05; 95% CI 0.86-1.29).[173]

Adjusted mortality rate ratios for all cancers (0.83, 0.66-1.05) were lower in US Gulf War veterans three years post Gulf War, although the difference was not significant.[192] In the seven year follow-up study, there were no significant excess of overall cancer deaths (OR 0.90, 95% CI 0.81-1.01) or deaths from cancer at any specific site among male US Gulf War veterans compared with non-Gulf veterans.[109] Cancer accounted for 53 deaths in the British Gulf War cohort and 48 in the Era cohort, but this difference was not significant and not related to any single type of cancer.[193]

In their review of 20,000 veterans who had been evaluated by the CCEP, Joseph *et al*[19] found that 22 (0.1%) veterans were diagnosed with lymphoma/leukaemia and 30 (0.15%) with other types of cancer. There has been concern over the numbers of cases of cancers, in particular lung cancers and leukaemia, in veterans of both the Gulf War and the Balkan War,[241-243] but no excesses have been found in epidemiological studies.[244]

Rates of self-reported 'any cancer' (prevalence difference 0.8; 0.2-1.4) and of 'skin cancer' (prevalence difference 0.8; 0.4-1.3) were only marginally elevated in the Gulf War compared with the non-Gulf War group.[16] Kang *et al*[20] found similar self-reported findings in US veterans, with the rate difference for 'other cancer' of 0.18 (0.15-0.21) and for 'skin cancer' of 0.15 (0.11-0.19).

4.19 Hospitalisations, medical care utilisation due to illness, functional impairment and limitation of work

Gray *et al*[188] conducted a retrospective cohort study of postwar risk of hospitalisation experience among 547,076 Gulf War veterans and 618,335 active duty veterans from the same era who were not deployed to the Gulf War. The overall rate of hospitalisations after the war was not higher than that for the comparison group, even after adjustment for selection biases that may have resulted from deploying the healthiest people to the Gulf War, assessed through consideration of prewar hospitalisation risk. Age and sex-adjusted postwar attrition of Gulf War veterans was higher than non-deployed veterans but the difference was not due to disqualification due to medical reasons (standardised rate ratio (SRR) 0.81; 0.79-0.83) or mortality (SRR 1.03; 0.93-1.14). Overall risk of hospitalisation was increased among women, health care workers, persons with the lowest salaries and married, older, white, Army or enlisted personnel. The risk of hospitalisation in 16 of the 42 comparisons involving specific diagnoses among Gulf War veterans differed significantly from that among non-deployed veterans. Gulf War veterans were at higher risk in 5 of these comparisons: neoplasms during 1991 (largely benign, although the risk for testicular cancer was slightly elevated during 1991 but did not persist 4 years after deployment), diseases of the genitourinary system during 1991, diseases of the blood and blood-forming organs during 1992 (mostly forms of anaemia, and primarily thought to be associated with pregnancy), and mental disorders during 1992 and 1993 (significantly more frequently for conditions related to alcohol and drug use and for adjustment reactions). The differences were not consistent

over time, and were considered to be accounted for by deferred care, postwar pregnancies, chance and postwar stress.[188]

Gray *et al*[187] built on their previous study[188] to include reserve and separated military personnel who may have been hospitalised in non-Department of Defense hospitals. The proportional morbidity ratios (PMRs) of hospitalisation discharge diagnoses, for three hospital systems, between Gulf War veterans and veterans of the same era, were compared. Gulf War veterans experienced proportionally more hospitalisations for a number of specific diagnoses, ie increased hospitalisations for injury and poisoning in the Department of Defense system (PMR 1.03; 95% CI 1.01-1.05) and in the California Office of Statewide Health Planning and Development system (PMR 1.11; 95% CI 1.04-1.18); respiratory system including asthma (PMR 1.19; 1.10-1.29), digestive system (PMR 1.12; 95% CI 1.05-1.18), and symptoms, signs and ill-defined conditions (PMR 1.24; 95% CI 1.16-1.33) in the VA hospital system. Gulf War veterans experienced proportionally lower or proportionally similar hospitalisation for other diagnostic categories of infectious and parasitic diseases, neoplasms, endocrine diseases, blood diseases, nutritional and metabolic diseases, mental disorders, or diseases of the blood, nervous system, circulatory system, genitourinary system, skin and musculoskeletal system across the three hospital systems.[187]

The post war hospitalisation experience of US Gulf War veterans, who were near Khamisiyah, Iraq during the destruction of nerve agent munitions in March 1991, was examined using US Department of Defense hospital data and an exposure classification based on modelling of plume estimates overlaid on military unit positions.[107] No evidence was found to indicate that possible nerve agent exposure was associated with postwar hospitalisation risk for any of the 15 major ICD-9 categories examined or for diagnoses that an expert panel had suggested to be possible neurological sequelae of subtle nerve agent-induced, neurophysiological effects such as mononeuritis, peripheral neuropathy, myoneural disorders and myopathies. In only one of 32 additional models used, were possibly exposed veterans at slightly increased risk of hospitalisations due to mental disorder diagnosis. This increased risk appeared to be due to mental disorder diagnoses' adjustment reaction and nondependent use of drugs. A dose response relationship was not suggested by any of the models used.[107]

Knoke and Gray[186] conducted a retrospective cohort study of postwar risk of hospitalisation for unexplained illnesses among 552,111 US Gulf War veterans and a comparison group of Gulf War era military personnel. Deployed veterans had a slightly elevated risk of hospitalisation for unexplained illnesses than the non-deployed subjects (RR 1.08, 95% CI 1.05-1.11), with most of the excess hospitalisations for the Gulf War veterans due to the most non-specific of the diagnostic categories "illness of unknown cause" (ICD-9 code 799.9). The increased risk in Gulf War veterans was thought to be due to the effect of CCEP hospitalisation, which were mostly for medical evaluation rather than for clinical management; as when the subjects hospitalised under the CCEP were excluded from the analyses, the risk for an unexplained illness was generally lower in the deployed than the non-deployed subjects (RR 0.93, 95% CI 0.91-0.96).

In a large US cross-sectional study, Gulf War veterans had a higher prevalence of functional impairment, ie stayed in bed or at home for all or part of any day because they did not feel well or as a result of illnesses or injury in the last 2 weeks (27.8% vs 14.2%; crude rate ratio 1.96; 95% CI 1.85-2.07); a higher prevalence of hospitalisation overnight or longer in the previous year (7.8% vs 6.4%, crude rate ratio 1.22; 95% CI 1.10-1.34); limitation of employment because of any impairment of health problems (17.2% vs 11.6%, crude rate ratio

1.48; 95% CI 1.38-1.56); and health care utilisation, ie clinic visit because of illness during the previous year (50.8% vs 40.5%; crude rate ratio 1.25 1.22-1.29). Perception of general health status between the groups was significantly different, with 15.9% of Gulf War veterans reporting that their health was excellent and 43.4% reporting that their health was excellent or very good compared with 30.1% and 67.1% of non-Gulf veterans respectively.[20]

Cherry *et al*[157] found high rates of hospital referral by their general practitioner in Gulf War and non-Gulf groups (approximately 50%) and no evidence of an important excess in Gulf War veterans. However, for the same level of reported ill-health, Gulf War veterans were less likely to be referred to specialists than non-Gulf veterans.

4.20 Mortality

During the Gulf War, US casualties were comparable to those of US troops stationed elsewhere.[245, 246] There were no clusters of unexplained deaths during the war itself.[245]

Kang and Bullman conducted a retrospective cohort mortality study of all 695,516 Gulf War veterans and a comparison group of almost half of all military personnel on active duty in the National Guard and in the military reserves who served from September 1990 to April 1991 but who did not go to the Gulf (n=746,291), and reported the 3 year and 7 year follow-up findings.[109, 247]

In the 3 year follow up study, a small but significant excess of all cause mortality among the Gulf War veterans compared with the non-Gulf War veterans (adjusted rate ratio 1.09; 95% CI 1.01-1.16) was mainly caused by accidents (1.25; 1.13-1.39) rather than disease (0.88; 0.77-1.02). Adjusted mortality rate ratios for infectious and parasitic disease (0.21, 0.11-0.43), all cancers (0.83, 0.66-1.05), and disease of digestive system (0.79, 0.37-1.69) were lower in Gulf War veterans although the differences were not significant. Among 49,919 female veterans of the Gulf War, the corresponding rate ratios were death from all causes (1.32; 0.95-1.83), accidental death (1.83; 1.02-3.28) and disease-related deaths (0.89; 0.45-1.78). The adjusted standardised mortality ratios for Gulf War veterans 0.44 (0.42-0.47) and other veterans 0.38 (0.36-0.40) were significantly lower overall than those in the general population.[247]

In the 7 year follow up study, male Gulf War veterans had slightly lower risks of both overall mortality (adjusted RR 0.95; 95% CI 0.92-0.99) and mortality due to natural causes than male non-Gulf-war veterans (0.83; 0.78-0.99). The lower risk of death from natural causes was attributed mainly to the relatively higher number of HIV-related deaths among non-Gulf veterans (0.21; 0.15-0.30). However, the risk of death from disease-related causes had steadily increased over the last three follow-up periods and, in the last follow-up period, the risk was almost identical in the two cohorts (0.97; 0.86-1.08). Among Gulf War veterans, the significant excess of deaths due to motor vehicle accidents observed in the 3 year follow-up study had decreased steadily from a rate ratio of 1.32 (1.13-1.53) in the first follow-up period to a rate ratio of 1.00 (0.82-1.22) in the last follow up period, but was still significantly higher overall (1.19; 1.09-1.30). 48,281 Gulf veterans were identified as likely to have received at least subclinical exposure to nerve gas, sarin or cyclosarin. However, there were no statistically significant differences in all-cause or cause-specific mortality among Gulf War veterans relative to potential nerve gas exposure. There was no significant excess of overall cancer deaths (0.90; 0.81-1.01) or deaths from cancer at any specific site among male Gulf War veterans compared with male non-Gulf veterans. The risk of death for both Gulf War veterans (standardised mortality ratio 0.41; 0.40-0.42) and non-Gulf veterans (0.42; 0.41-0.43) remained less than half that expected in the general population.[109]

Macfarlane *et al*[193] conducted a retrospective cohort mortality study of all 53, 462 UK Gulf War veterans and a randomly selected stratified comparable group of military personnel in the services at the time of the Gulf War but who did not go to the Gulf. There were 395 deaths among the Gulf cohort (0.74%, 94 deaths per 100,000 person-years) and 378 deaths among the Era cohort (0.71%, 90 deaths per 100,000 person-years). The overall mortality rate ratio was 1.05 (0.91-1.21). Mortality rates were highest in the Gulf War group, compared to the comparison group cohort, for males (1.05; 0.91-1.22); officers (1.14; 0.78-1.66); and those serving in the Royal Navy (1.33; 0.83-2) or Royal Air Force (1.32; 0.93-1.88). Mortality from external causes was higher in the Gulf cohort (1.18; 0.98-1.42). The highest excess mortality was noted for motor vehicle accidents (1.25; 0.91-1.72). Disease-related mortality was lower in the Gulf cohort (0.87, 0.67-1.11). Cancer accounted for 53 deaths in the Gulf cohort and 48 in the Era cohort, but this difference was not significant and not related to any single type of cancer.

It has been suggested that the postwar excess injury risk reported in the US and British mortality studies[192, 193] may be explained by a propensity for risk taking behaviour considered to be evident before the war and which may have persisted after the Gulf War.[248]

4.21 Self-referral evaluation programs

Most of the discussion so far has centred around the epidemiological studies that are most directly relevant to the Australian study. However, the US and UK clinical assessment and evaluation programs have played an important role in Gulf War health research, and are discussed here.

The self-referral evaluation programs and registries were of value in providing the opportunity for veterans with health concerns to obtain a comprehensive physical examination, baseline laboratory investigations and referral for specialist assessment and follow-up as necessary. The large case series evaluations had sufficient statistical power to detect small differences, and the potential for geographic and occupational bias was reduced because data was collected from medical centres throughout the United States. The evaluations provided valuable clinical data for defining conditions and generating research hypotheses for examination in analytical studies. However, there were many limitations to this approach. The main limitation is that registry participants were not representative of the personnel deployed to the Gulf War, and were probably not representative of the veterans who were sick. The participants were self-selected and concerned enough about the possible adverse effects of their service in the Gulf War to attend the Department of Veterans Affairs or Department of Defense medical centres for an examination. In addition, there was no data on a non-Gulf veteran comparison group, risk factors could not be examined and the results were limited in their generalisability.

The US established two separate clinical assessment programs - the Department of Veterans Affairs Persian Gulf Registry (VA Registry) in August 1992, for people who had left the armed forces after serving in the Gulf War; and the Department of Defense Comprehensive Clinical Evaluation Program (CCEP) in June 1994, for service personnel on active duty.[19] Eligible veterans were self-referred. The CCEP provided a systematic and comprehensive evaluation through a two-phase clinical evaluation, with specialist consultation and testing if necessary, in order to establish a diagnosis. Diagnostic codes (one primary and up to 6 secondary) were then assigned according the ICD-9-CM. About 14% of the US Gulf War veteran population has been evaluated through these programs.[192] The British Ministry of Defence established a similar program, the Medical Assessment Programme (MAP), in

October 1993.[185] Several large case series evaluations of between 13,000-20,000 US veterans[17, 19, 33, 43, 182] and two sequential case series evaluations of 1000 British veterans have been conducted.[183, 184]

The symptoms most commonly reported by CCEP participants were joint pain (50.0%), fatigue (46.9%), headache (39.7%), memory or concentration difficulties (34%), sleep disturbances (33.0%), rash (30.2%),[33] and this pattern was similar to that of the VA Registry.[17] Headache, fatigue, joint pain, fatigue and rash were symptoms that were more likely than others to be the chief complaint (at least 20% of the time). The onset of symptoms was often delayed. Two-thirds of symptoms developed after return from the Gulf and 40% had a latency period exceeding one year. Participants seldom recalled symptoms as predating the war (usually less than 5%).[33]

As a primary diagnosis, the most common broad diagnostic categories were "musculoskeletal and connective tissue" (18.6%), "mental disorders" (18.3%), "symptoms, signs and ill-defined conditions" (17.8%), "diseases of the respiratory system" (6.8%), "diseases of the skin and subcutaneous tissue" (6.3%), "diseases of the digestive system" (6.2%) and "diseases of the nervous system and sense organs" (5.8%).[19] The pattern was similar to that reported in other US registry evaluations.[33, 182] Joseph *et al*[19] emphasised that the ICD-category "symptoms, signs and ill-defined conditions" was not a mystery illness, but contained over 160 subcategories that consisted mainly of ill-defined, often common conditions not coded elsewhere, isolated laboratory abnormalities, and common symptoms that do not have a clear physiological or psychological basis. Of the 17.8% of veterans who were diagnosed with "symptoms, signs and ill-defined conditions", 26.6% had malaise and fatigue as a diagnostic subcategory.[19]

Less common diagnoses were "infectious and parasitic diseases" in 2.6% of veterans (for which common skin infections accounted for 60%), connective tissue disease as either a primary or secondary diagnosis in 0.4% of participants, disorders of immunity in 5 participants, skin cancers in 9 (0.05%), lymphoma/leukaemia in 22 (0.1%), other types of cancer in 30 (0.15%), interstitial pulmonary fibrosis in 14 (0.07%), glomerulonephritis in 13 (0.07%) and renal insufficiency in another 12 (0.06%) patients.[19] Polyneuropathy or peripheral neuropathy was diagnosed in 8 and 34 (0.2%) of veterans respectively. For over 800 veterans with neuromuscular symptoms who had extensive neuropsychological evaluations, a common or distinctive organic pathology was not identified. The types of physiological disease that could have resulted from possible war time exposures such as neurologic disease from possible chemical warfare or pesticide exposure, interstitial pulmonary disease from smoke or sand inhalation, renal disease from heavy metal exposure, and immunological dysfunction from various combinations of exposures were uncommon.[19]

Of the 13,161 veterans evaluated in the first year of the CCEP, 37% had at least one psychological condition. Comorbidity was common; and 64% of those with a psychological condition had one, 25% had two, and 11% had three or more additional psychological conditions. Somatoform disorders (14.3%), anxiety (8.1%) and mood disorders (12.6%) were the most common psychological conditions diagnosed. Psychological conditions were related to higher number of lost workdays. Stressful war experiences were weakly but significantly related to an increase in the number of psychological conditions.[43]

Registry participants were more likely to have been in the Army, National Guard or Reserve, and more likely to have been stationed in the Gulf War theatre during the fighting, to be older, to have had an enlisted rank, to have been construction workers, to be female and to have been hospitalised during the 12 month period preceding the Gulf War.[182] A high

proportion of registry participants (30.6%) were given no diagnosis (including 22.8% of VA registry participants for whom the principal diagnosis, after evaluation, was that no diagnosis other than "symptoms, signs and ill-defined conditions") or that of a healthy status, and were described as "the worried well".[182]

Medical conditions categorised as 'Diseases of the musculoskeletal system and connective tissue' were the commonest diagnosis in the US programs, diagnosed in 19-47% of people as a primary or a secondary condition,[19, 33, 182] and were also commonly diagnosed in the British program in 6-18% of participants.[183, 184] A more detailed investigation of the nature of these diagnoses, and the quality of life, in a case series of 145/928 US veterans referred for rheumatology evaluation found that the most common diagnoses were fibromyalgia (33.8%), various soft tissue problems (17.2%), non-specific arthralgias (9.6%) clinical or radiographic osteoarthritis (11.0%) and normal history and examination (26.9%). No specific diagnosis characterised Gulf War veterans, but pain was a common symptom and was widespread in distribution, and quality of life had been affected.[249] Similar diagnoses, although the proportions varied, were found in other case series.[250, 251]

Of the first 1000 UK Gulf War veterans seen in the British MAP between October 1993 and February 1997, 588 (59%) had more than one diagnosed condition, and 387 (39%) had at least one condition for which no definite somatic or psychological diagnosis could be given, and in 90 (9%) no other main diagnosis was made. Conditions characterised by fatigue (24%), psychiatric conditions (19%) with over half of those due to posttraumatic stress disorder, musculoskeletal disorders (18%) and respiratory conditions (16%) were common.[184] Thirty-nine (3.9%) had a diagnosis of alcohol misuse and 10 (1%) had a diagnosis of drug misuse.[184]

The most common symptoms were affective symptoms (49%), fatigue (42%), joint and muscle pain (40%), cognitive symptoms (26%), headaches and migraines (26%), respiratory complaints (24%), gastrointestinal problems (22%), sleep disturbances (21%), and rashes, skin problems and hair loss (19%). If the patients with symptoms of fatigue, lethargy or malaise were combined with those with a diagnosis of chronic fatigue syndrome, 239 (24%) of patients had a main condition characterised by fatigue.[184]

An increased percentage, 796 patients (80%), of the second 1000 MAP participants who presented between February 1997 and February 1998 were well, and although many had symptoms or organic disease they were functioning normally. Ten percent were completely well, ie asymptomatic, 38% were well with symptoms but no disease; and 25% were well with incidental diagnoses of identified organic disease (of whom 16 also had a psychiatric disorder). Five per cent had both organic and psychiatric conditions, and 20% of patients were considered to be unwell. Fewer participants {2 (0%) vs 387 (39%)} were coded as "ill-defined symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified".[183] Two hundred and fifty-two (25%) had psychiatric conditions which remained active in 173 (69%). The remaining 79 (31%) now well, had psychiatric disorders following Gulf service. The principal psychiatric diagnosis was posttraumatic stress disorder in 87 (9%), compared with 115 (12%) in the first 1000, and the majority arose as a result of Gulf War service. Ninety-one (9%) were diagnosed with depression compared with 49 (5%) in the first 1000. The most common Gulf related illnesses were psychiatric, and the most frequent were PTSD with or without comorbidity. The symptom prevalence was consistently greater in those "unwell with psychiatric disorders" or "no formal psychiatric diagnosis" compared with the "well with symptoms" patients, although the distribution of overall symptoms was similar.

In summary, no single illness predominated,[19, 184] and there was no clinical indication of a new or unique syndrome pertaining to the Gulf War[19] or a single illness or condition, physical or psychological, that could explain the pattern of symptoms[184] or could be related to toxic exposures.[33] Many Gulf War veterans had a wide variety of conditions and often more than one condition,[184] and there was a tendency to report multiple symptoms.[33, 184] A substantial proportion had conditions that were not readily diagnosable or classifiable.[33, 184] Although the proportions of symptoms or conditions varied, and direct comparisons were not possible, similarities between the main findings of the British and US programs were noted.[184] The pattern of symptoms or disease was considered similar to that seen in primary care practice[183] or the general population[33] and similar to other post conflict illnesses.[183, 184] Symptoms did not equate with ill-health, however, the more symptoms the greater the likelihood of a psychiatric disorder.[183] Joseph *et al*[19] acknowledged that the causes, frequency and long-term implications of nonspecific somatic symptoms that are common in the general adult population are not well understood, and whether these symptoms represented transient conditions or were an expression of underlying organic disease or psychological illness was difficult to determine.[19]

4.22 Summary

The published Gulf War medical research literature is enormous and continues to develop, and it is impossible to summarise this entire body of literature with any justice in a few pages. Therefore, in this chapter we have focussed on a tabulation and discussion of the major epidemiological and other studies that are most relevant to the aims of the Australian study. The main findings of these studies and their relevance to the development of our study can be summarised as follows.

On the basis of self-reported health outcomes, Gulf War veterans do not appear to be as healthy as the military service populations they have been compared to, including populations exposed to other hostile warlike environments such as deployment to Bosnia. A unique health outcome or syndrome has not been identified amongst Gulf War veterans, and no specific Gulf War experience or exposure has been uniquely or causally implicated in, or accepted as, an explanation for the health outcomes reported by Gulf War veterans. A more general effect of war or conflict on self-reported health has been postulated as an explanation.

A consistent finding in the cross-sectional studies has been an increased reporting of multiple symptoms by Gulf War veterans compared to the non-Gulf comparison populations. The order of frequency of health symptoms reported by Gulf War veterans and the comparison groups has been similar. Patterns have emerged in the reporting of symptoms relating to particular body symptoms. Symptoms suggestive of peripheral neuropathy, widespread pain, symptoms of fatigue and chronic fatigue, neuropsychological or neurocognitive symptoms, and gastrointestinal symptoms have all been more commonly reported by Gulf War veterans than non-Gulf comparison groups.

The pattern of self-reporting of an increased number of medical conditions is similar to that of symptoms, although not as consistent or marked. Gulf War veterans have reported many, if not all, of the medical conditions more commonly than non-Gulf veterans. There are similarities in the symptomatology and medical conditions reported by UK and US veterans.

Several studies of Gulf War veterans have also reported greater functional impairment and health care utilisation, a lower general health perception, and diminished mental and physical functioning on standardised measures such as the SF-36, when compared to a similar group of military service personnel.

Factor analysis of self-reported symptoms in the cross-sectional studies has been used to investigate whether this increased reporting of non-specific health symptoms constitutes a new disorder or syndrome. The findings across studies using factor analysis, which have employed a comparison group, have generally been consistent, and do not support the concept of a unique illness amongst Gulf War veterans.

In Gulf War veterans health research internationally, a variety of specific health outcomes have been the subject of study, including psychological health, respiratory health, neurological health, infectious diseases, chronic fatigue and the immune system, musculoskeletal, dermatological and gastrointestinal systems. Some of the overall findings that relate to these health outcomes are summarised here.

An important area of study has been psychological health. Historically, many studies have shown that the experience of war, and the subsequent transition from military to civilian life, can have legacies that manifest themselves in a variety of physical and psychological health problems. Higher than expected rates of psychiatric conditions and unexplained physical symptoms in Gulf War-exposed groups have been consistent findings of overseas studies. In general though, Gulf War studies have been limited in their investigation of the possible causes of psychological distress in Gulf War veterans. In the current scientific literature, the overall picture of psychological morbidity in Gulf War veterans, and related exposures, is a complex one. Common themes appear in findings of increased depressive, anxiety and PTSD-related symptoms, alcohol or substance misuse and multiple non-specific psychological symptoms. There is some evidence, although this is not consistent, that these psychological health outcomes are possibly associated with levels of combat severity and unit resourcing, combined with levels of rank or seniority, younger age, training, combat experience and personal resourcefulness.

Respiratory tract complaints were a common, although generally non-debilitating, source of morbidity during the Gulf War. Respiratory symptoms and respiratory medical conditions have been significantly more commonly reported by Gulf War veterans in cross-sectional studies conducted since the Gulf War, and 'Diseases of the respiratory system' have been a common diagnosis in registry participants. Clinical evaluation of the association between self-reported exposures such as SMOIL and respiratory medical conditions is limited, and the long term effects of SMOIL are not known. There is very limited objective evaluation of respiratory function using measures such as spirometry, in the cross-sectional studies using representative populations.

Mild cases of acute respiratory or gastrointestinal infections were a cause of morbidity during the Gulf War. Infectious diseases as a cause of Gulf War related illnesses have been widely considered, and some hypotheses, relating to a possible contribution of infectious agents to illnesses in Gulf War veterans, are currently being investigated. Large epidemiological studies of Gulf War veterans have not shown increased rates of hospitalisation or mortality from infectious diseases. Overall, researchers have concluded that it is unlikely an infectious process could cause significant long term health problems and remain undetected, particularly as no consistent pattern of objective signs or laboratory abnormalities to indicate an infectious process, has been found.

Neurological and neuropsychological symptoms, neurological conditions, and a pattern of symptoms suggestive of peripheral neuropathy have been reported more commonly by Gulf War veterans than by their comparison groups. A more detailed and quantitative evaluation of the neurological health of Gulf War veterans has had recognised methodological limitations that limit the conclusions and the generalisability of results. An increased case

rate of motor neurone disease in US Gulf War veterans compared to non-deployed veterans has been reported, but the evidence has not been published in the medical literature.

Musculoskeletal, dermatological and gastrointestinal symptoms and conditions have been reported more commonly by Gulf War veterans. A number of veterans who have retained metal fragments are being followed up on a long term basis for DU related health problems. No major DU related health problems have been detected or reported to date. The rates of self-reported cancers in cross-sectional studies of Gulf War and non-Gulf veterans have been similar.

The differences in health status between Gulf War veterans and non-Gulf comparison groups are less apparent in the findings of studies that are less subject to possible recall bias through self-report. These studies are based on retrospective reviews of health records of reproductive outcomes, or data in cancer and mortality registries.

Whilst higher rates of miscarriages have been reported by male Gulf War veterans and higher rates of birth defects have been reported by male and female Gulf War veterans in one study based on self-report, the potential for reporting bias has been acknowledged and a review of medical records proposed. Retrospective reviews of birth records have found no excess of adverse reproductive health outcomes among births to Gulf War veterans, and the risk of birth defects was comparable to that of the general population.

Gulf War veterans have been found to be at a higher risk of neoplasm during the immediate postwar period (largely benign neoplasms) but not during subsequent years, and an early elevation in the risk of testicular cancer did not persist by four years after the end of deployment. There was no significant excess mortality rate for cancer 3 years and 7 years follow-up post deployment.

The overall rate of hospitalisations after the war have not been found to be higher in Gulf War veterans than the comparison groups, and there is no evidence that US Gulf War veterans who were near Khamisiyah, Iraq during the destruction of nerve agent munitions in March 1991 were at increased risk of hospitalisation.

A small but significant excess of all-cause mortality was observed among US Gulf War veterans compared to non-Gulf veterans, three years post deployment, but not among UK Gulf War veterans. Both UK and US Gulf War veterans were at higher risk of mortality from external causes rather than disease, and this was mainly due to motor vehicle accidents. For US veterans, this excess had decreased to the level of non-Gulf veterans by the 7 year follow up post deployment. In both periods, the risk of death for US Gulf War veterans remained less than half that of the general population.

Registry or clinical evaluation programs have examined and diagnosed thousands of individual Gulf War veterans and reported on their findings. No single illness predominated, and no clinical indication of a new or unique syndrome or condition that could explain the pattern of symptoms or could be related to toxic exposures has been identified.

There are many limitations in the published studies of Gulf War veterans' health. The cross-sectional studies have generally not had the opportunity to undertake medical examinations or more objective or quantitative measurement of health outcomes as part of the study, in order to validate self-reported health outcomes. For example, in relation to respiratory, neurological and psychological health, objective measures such as spirometry, a physical examination by a doctor, and an interview conducted by a psychologist respectively can provide valuable objective measurement of health. Those studies that included objective

measures have been undertaken on relatively small groups of veterans, non-representative populations or registry participants.

There are a number of possible exposures in the Gulf War that have been associated with adverse health outcomes, and have been considered variously in many of these studies. The exposures for which there has been some consistency in their association with adverse health outcomes includes combat experiences and trauma, the perceived threat of biological and chemical warfare, environmental and chemical exposures such as SMOIL, pesticides, insect repellents, DU, and medical exposures such as vaccinations (both routine and biological warfare, and multiple vaccinations particularly during deployment) and pyridostigmine bromide. Rank is the main occupational factor that has been associated with psychological and physical ill-health. Age, service type, branch and type of service have also been associated with adverse health effects.

However, there is usually limited objective or quantitative exposure assessment data available; even when sophisticated computer modelling is utilised. Information on proposed toxic aetiologies such as pyridostigmine bromide, use of topical insecticides and flea collars, exposure to depleted uranium, smoke from oil well fires and vaccinations have usually been collected by self-report with little opportunity to validate these. The exposures considered most relevant to consider, based on those reported in international studies, the particular circumstances of the Australian deployment to the Gulf War and scientific and biological plausibility, are described in more detail in chapter 3.

In summary, international research into the health of Gulf War veterans has faced a number of limitations including health outcome data based on self-report or in self-referred populations; difficulties in measuring exposures and limited objective data for verifying exposures; difficulties contacting study participants and low response rates, particularly for control groups; and limited comparability of health outcomes between studies because of the different instruments used and differences between the populations studied.

5. Cross-sectional study methods

5.1 Aims and objectives

The Australian Gulf War Veterans' Health Study was designed to investigate whether Australian Defence Force personnel who served in the Gulf War have a higher than expected rate of several adverse health effects; and, if so, whether these effects are associated with exposures and experiences that occurred in the Gulf War.

Therefore, the specific research null hypothesis to be addressed was:

> *'The health (both physical and psychological) of Australian veterans of the Gulf War does not differ significantly from similar Defence Force personnel who were not deployed to the Gulf War.'*

Within this overall hypothesis are several specific research questions that the study was designed to answer:

- Do Australian Gulf War veterans have increased prevalence of psychological disorders including depression, anxiety and substance disorders; and if so, are these associated with exposures and experiences that occurred in the Gulf War?
- Do Australian Gulf War veterans have increased prevalence of symptoms, symptom clusters and medical conditions, related to several body systems; in particular psychological, respiratory, neurological; musculoskeletal and skin, and if so, are these associated with exposures and experiences that occurred in the Gulf War?
- Do Australian Gulf War veterans have increased prevalence of chronic fatigue syndrome; and if so, is this associated with exposures and experiences that occurred in the Gulf War?
- Do Australian Gulf War veterans have significantly lower lung function than expected; and if so, is this associated with exposures and experiences that occurred in the Gulf War?
- Do Australian Gulf War veterans have an increased prevalence of laboratory test results that are indicative of adverse health effects, including evidence of increased rates of markers of infection; and if so, are these associated with exposures and experiences that occurred in the Gulf War?
- Do Australian Gulf War veterans have an increased risk of having a child with a major congenital malformation or increased risk of childhood cancer, or have an increased risk of infertility, following return from the Gulf and, if so, are these associated with exposures and experiences that occurred in the Gulf War?
- Do Australian Gulf War veterans have increased rates of cancer and mortality?

5.2 Study design

The Australian Gulf War Veterans' Health Study was designed to:

- Establish a cohort of Australian Gulf War veterans to determine all-cause mortality and cancer incidence rates using data from the National Death Index and the National Cancer Statistics Clearing House. This cohort can be followed prospectively to measure cancer and mortality experience and to monitor other health indicators.
- Undertake a cross-sectional study of this Gulf War veterans' cohort and a frequency matched comparison group to investigate the other research questions of the study.

This chapter describes the methodology for the cross-sectional study. The mortality and cancer incidence cohort study is described in chapter 17.

5.3 Study population

5.3.1 Definition of the Gulf War veteran group

The Gulf War veteran group has been defined as all Australian Defence Force (ADF) personnel, from the Royal Australian Navy, Royal Australian Army, and the Royal Australian Air Force, who served in the Gulf War and who are listed on the Department of Veterans' Affairs Nominal Roll for that conflict. To be included on the Nominal Roll an ADF member must have been deployed to the Gulf sometime during the period 2 August 1990 to 4 September 1991.

The Nominal Roll includes:

- ADF personnel on temporary as well as permanent postings. The majority of ADF members listed on the Nominal Roll deployed as part of Operation Ozone and Operation Damask, or with overseas forces as part of Operations Desert Shield and Desert Storm.
- Personnel who were members of the Navy, Army or Air Force Reserves.
- Personnel on board the second deployment of HMAS Darwin which reached the Gulf just after the war ended, serving from 13 June 1991 to 4 September 1991.
- Personnel who went to Kurdistan in northern Iraq as part of Operation Habitat to provide humanitarian aid from 16 May 1991 until 30 June 1991.
- Operation Blazer personnel who deployed to Iraq immediately after the war ended in support of the United Nations Special Commission (UNSCOM) to oversee the destruction of weapons of mass destruction.
- Support personnel who deployed to the Middle East to provide logistic support to the ships and aircraft. These include personnel from the Royal Australian Air Force (RAAF) Mobile Air Terminal Unit (MATU), and the Navy Logistic Support Element (LSE).

The Nominal Roll does NOT include:

- Those personnel who were on other Defence duties in the Middle East at the time of the Gulf War and who were deployed in support of other Defence duties or United Nations (UN) peacekeeping operations. These include personnel serving with the UN Truce Supervision Organisation (UNTSO) in Beirut, South Lebanon, Israel and Syria as well as those deployed as part of the Multinational Force and Observers (MFO) in the Sinai.
- Subjects who were in non-Defence roles in the area of the Gulf, for example embassy personnel and reporters.
- Personnel deployed to UNSCOM as part of Operation Blazer after 4 September 1991.
- Personnel deployed to the Gulf and the Red Sea in support of Operations Damask IV - IX after 4 September 1991.

5.3.2 Definition of the comparison group

Comparison group subjects for this study were defined as Australian Defence Force personnel who were operational in the Royal Australian Navy, Royal Australian Army or Royal Australian Air Force at the time of the Gulf War, eligible to be deployed to the Gulf, but either not sent to the Gulf or not otherwise eligible for inclusion on the Gulf War Nominal Roll according to the criteria provided above.

To identify the eligible comparison group two lists were compiled: one list of ADF personnel posted to Maritime, Land or Air Operational Units as at 1 August 1990 and a second list of those posted to Maritime, Land or Air Operational Units as at 1 August 1991. This included personnel on either permanent postings or temporary attachments to ships, units or squadrons including members of the Navy, Army or Air Force Reserves. The two dates were selected to ensure that those personnel who were posted to operational units during the period of the Gulf War were not missed for comparison group selection. The lists were merged and then Gulf War veterans, as defined by their inclusion on the Gulf War Nominal Roll, were removed leaving a total, eligible comparison sample of 5481 Navy, 6481 Army and 14494 RAAF personnel.

From the total eligible comparison sample for each service type, subjects were randomly selected using frequency matching to the Gulf War veteran group to achieve the sample sizes described below. The criteria used for the frequency matching varied across Service type. Navy comparison group subjects were matched with Navy Gulf War veteran group subjects according to sex and 3-year age bands. The rank distribution, within the Army units which were deployed to the Gulf War, was considered not representative of the larger Army operational force, and therefore the Army comparison group subjects were matched with Army Gulf War veteran group subjects according to sex, year of birth and two service rank categories ('Officer' and 'Other ranks'). Similarly the distribution of personnel in aircrew versus non-aircrew roles, within the Air Force units which were deployed to the Gulf War, was considered not representative of the larger Air Force operational force, and therefore the Air Force comparison group subjects were matched with Air Force Gulf War veteran group subjects according to sex, year of birth and the two job categories Aircrew and Non-Aircrew.

5.4 Sample size

5.4.1 Gulf War veteran group

At commencement of the Australian Gulf War Veterans' Health Study the Gulf War Nominal Roll totalled 1873 people. Of these, 1581 were from the Navy (including 8 known deceased), 123 were from the Army (including 1 known deceased) and 169 were from the Air Force (including 4 known deceased).

The entire Nominal Roll list was included in the Gulf War veteran group. Inclusion of the entire cohort was considered both feasible by the study team and necessary to maximise the study's potential to evaluate differences between the Gulf War veteran group and the comparison group and to allow subgroup analyses within the Gulf War veteran group.

5.4.2 Comparison group

The comparison group sample size was initially chosen to equal the size of the Gulf War veteran group of 1873 subjects. It was calculated that a recruitment rate of 80% per group would result in approximately 1500 Gulf War veteran and 1500 comparison group subjects participating in the study. With this number of subjects providing symptom information, the study was estimated to have at least 90% power, at a two-sided 5% significance level, to detect increases in the prevalence of symptoms in Gulf War veterans of the order of 20% to 100% (corresponding to odds ratios of 1.3 to 2.0) for symptoms with a prevalence of 2% to 30% (in reverse order) among the comparison group.

After six months of recruitment, it was determined that an 80% recruitment rate could be achieved for the Gulf War veteran group but that only a 60% recruitment rate could be achieved for the comparison group. Based on these revised recruitment forecasts, the

comparison group sample size was increased by randomly sampling additional subjects so as to yield an equal number of eligible Navy comparison group respondents, and twice the number of Air Force and Army comparison group respondents, as compared with the Gulf War veteran sample. This was intended to bring the study power back in line with the original estimates and also allow a buffer in the event that the final recruitment rate was slightly lower than that forecast. The doubling of the Army and Air Force comparison group samples would also result in additional power to detect moderate to large effects when these small groups were analysed separately from the larger Navy group.

The Navy comparison group was further supplemented in response to the finding that approximately 11% of the original Navy comparison sample were ineligible to participate as they had been discharged from the RAN prior to 1 August 1990.

The final comparison group sample size totalled 3192 subjects with 2384 from the Navy, 338 from the Army and 470 from the Air Force.

5.5 Contact strategy and recruitment procedures

5.5.1 DVA-based Contact and Recruitment team

The provisions of the Federal Privacy Act (1988) required that Monash University and Health Services Australia (HSA) not be allowed access to DVA-held information pertaining to the names and addresses of the Gulf War veteran and comparison group subjects until those subjects consented to participate in the study. Thus a DVA-based Contact and Recruitment team was established. The role of the Contact and Recruitment team was to:

- Obtain and maintain current contact details for the Gulf War veteran and comparison groups.
- Undertake initial mail contact with eligible subjects.
- Follow-up subjects who did not respond to the initial mail contact by attempting phone and/or e-mail contact.
- Respond appropriately to the queries and concerns of eligible subjects so that they could make an informed decision about participating in the study.
- Record the outcome of the recruitment effort for each Gulf War veteran and comparison group subject. For example, record whether the subjects agreed to participate, declined participation, were overseas, not contactable and so on.
- Forward the personal contact details of subjects agreeing to participate to HSA.

5.5.2 Contact procedures

All eligible subjects were initially invited to participate via mailed invitation. Mailouts of invitation packages to Navy subjects commenced in September 2000, followed by mailouts to Air Force subjects commencing in February 2001 and mailouts to Army subjects commencing in May 2001. Generally, during these initial mailouts, invitation packages were mailed in batches of 300 per week and these went to subjects from both the Gulf War veteran group and the comparison group each week. Those subjects who did not respond to the initial invitation package, within two weeks of its dispatch, were sent a reminder information package.

Phone and if possible, e-mail contact was then attempted for those subjects who did not respond to the reminder invitation package within two weeks of its dispatch. Phone contact was attempted at a variety of times across the day, including on nights and at weekends, to ensure maximum contact success.

The initial invitation package contained:

- A personally addressed letter of endorsement from the Minister for Veterans' Affairs.
- A personally addressed letter of endorsement from members of the study Consultative Forum.
- A letter of invitation to participate in the study from the Monash University and HSA study team.
- The study Explanatory Statement.
- A copy of the study Consent Form.
- A page providing Freecall 1800 contact numbers for the Contact and Recruitment team and for the Monash University/HSA study team.

The complete set of these mailout materials is provided at Appendix 1.

The reminder package was identical to the initial package, with the exception that the Minister's letter was replaced with a personal letter from the Principal Investigator of the Monash University/HSA study team. This letter is also provided at Appendix 1.

If subjects did not wish to participate, they were asked to indicate this by phoning the Freecall 1800 contact number so that the Contact and Recruitment team knew that the invitation package had been received and so that reminder notices about participation would not be sent.

The initial set of address and phone contact details for study subjects, used by the Contact and Recruitment team, were those recorded as 'last known' on the Department of Defence Personnel Management System database. Where addresses or phone contact details proved to be incomplete or out of date, the Contact and Recruitment team carried out the following search procedures to identify current contact details:

1. Search the DVA Client Database.
2. Search the CD-ROM version of the Telstra White Pages.
3. Search addresses, provided by the Australian Electoral Commission, as listed on the most recent version of the Electoral Roll.
4. Search the DVA Client Database for possible relatives in the area listed for "Address on Enlistment" on the study database.
5. Check for new addresses, or addresses for any Next of Kin, on the relevant Department of Defence Personnel Management System database.
6. Forward invitation packages to ComSuper, from where packages were further forwarded on to study subjects if ComSuper held an address different to that known by DVA.
7. Request that the Health Insurance Commission (HIC) provide a more current address, if one was held, from the Medicare database.

When a new address was found, a new information package was dispatched and this was followed up with a reminder package and follow-up phone contact if necessary.

5.5.3 Methods to maximise participation

In an effort to maximise participation in the study, and in addition to the mailouts and follow-up efforts described above, the following strategies were employed:

- Promotion of the study via the mass-media including Ministerial press releases, television coverage, newspaper articles and advertisements in Defence-related publications,
- Informed promotion of the study by the Consultative Forum to the members of the organisations they represented,

- Presentations to the members of interested groups and associations,
- Liaison with Defence Force personnel to facilitate the location of serving Defence Force members. This included the logging of Ship locations and expected return dates to facilitate contact of deployed Navy subjects,
- Organisation of medical teams to conduct medical assessments at locations remote to the standard HSA offices. For example, medical assessments were conducted by assessment teams sent to Cairns in Queensland and to the Western Australian HMAS Stirling Naval base,
- Reimbursement of any loss of income incurred as a result of participation,
- Reimbursement of travel and accommodation costs incurred as a result of participation,
- Provision of vouchers for meals and refreshments during the course of attendance at the medical assessment,
- Agreement by the Department of Defence that serving Defence Force members be able to attend as part of their duties,
- Availability of flexible appointment times, including some late afternoon and Saturday appointments.

5.5.4 Participation options

Full participation in the study involved completing a written postal questionnaire and attending a medical assessment at a Health Services Australia (HSA) Clinic. The questionnaire was estimated to take up to two hours to complete and the medical assessment was estimated to take up to five hours with the inclusion of a break. Travel time to and from the HSA clinics varied considerably depending on a subject's residential address. In some cases, where the travel time was lengthy, participants were accommodated overnight.

Where subjects were willing to participate in the study, but were unable to undertake the travel or offer the time necessary for full-participation, they were offered the option of becoming a 'postal questionnaire only' participant. These participants completed the postal questionnaire but did not attend for the medical assessment. The postal questionnaire was forwarded to participants in the mail along with a reply-paid envelope for its return.

5.5.5 Telephone-questionnaire option

Subjects who were contacted but who declined to complete either the medical assessment or the postal questionnaire, were offered the option of completing a brief telephone-administered questionnaire. The telephone questionnaire (Appendix 2) contained the Short-Form-12 Health Survey (SF-12) (see section 5.6.1.3.1) and some demographics and lifestyle questions including country of birth, highest education level, occupational status and smoking history.

The telephone questionnaire was administered by the DVA contact and recruitment team, and also by HSA administrative staff.

5.5.6 Administration of appointments for medical assessments

When subjects agreed to fully participate in the study, by agreeing to undertake the medical assessment and postal questionnaire, their contact details were forwarded via weekly electronic dispatch to a designated recipient at the HSA Head Office in Canberra. HSA then undertook responsibility for arranging the completion of the postal questionnaires and the medical assessments according to the following procedure:

1. Upon import of the electronically transferred data, subject's postcodes were used to allocate individuals to that HSA office which appeared to be the closest to their home address. Study participants could be allocated to any one of ten HSA offices, these being located at:
   - Canberra ACT
   - Parramatta NSW
   - Newcastle NSW
   - Wollongong NSW
   - Surry Hills NSW
   - Melbourne VIC
   - Adelaide SA
   - Perth WA
   - Brisbane QLD
   - Darwin NT

   Tasmanian study participants were allocated to the Melbourne HSA office and flown to that office for their medical assessment. HSA also undertook some assessments in Cairns, Queensland and on the ADF Naval base HMAS Stirling in Western Australia.
2. Designated and trained administrative officers at each HSA office would then contact the study participant in order to arrange a suitable appointment time for the medical assessment.
3. The subject could be reallocated to a different HSA office if requested.
4. Once an appointment had been made, the administrative officer would mail an Appointment Confirmation package to the subject (Appendix 3). This included:
   - A letter with the appropriate appointment time and location;
   - An Instructions to Participants document requesting that the postal questionnaire be completed and brought to the medical assessment, and outlining the medical assessment requirements relating to the medical assessment, eg refraining from smoking one hour prior to the appointment;
   - Documentation required for claiming compensation for travel costs from DVA;
   - The study postal questionnaire.
5. Participants were then recontacted by phone, 24 - 48 hours prior to their appointment, to remind them of their appointment details and to answer any final questions about the requirements for the medical assessment or postal questionnaire.
6. Upon arrival at the HSA office for their medical assessment appointment, participants were seen first by a nurse, secondly by a psychologist and thirdly by a medical officer, as described in section 5.6.2.

5.6 Data collection instrumentation and measures

Full participation in the study involved two stages of data collection, with participants undertaking:

- completion of a postal self-administered questionnaire, and
- a medical assessment conducted by a trained HSA medical team, each comprising a nurse, clinical psychologist and medical doctor.

Where possible previously validated data collection instruments were used in the study, and the availability of normative comparisons was considered in the selection of instruments. Some instruments and the design of new questions were based on questionnaires used in overseas Gulf War studies, to allow comparisons where appropriate. For example the symptom questionnaire was based on the instrument used by the King's College Gulf War Illness Research Unit in London (with their permission and acknowledgment).

There was some intentional overlap in the assessment of important health outcomes. For example, symptoms of posttraumatic stress disorder and alcohol use were assessed in both the postal questionnaire and by psychological interview. Overlap of health assessments in this way enhanced the quality of data collection for health outcomes of particular interest and facilitated checks of data validity and reliability.

Equipment was standardised across HSA offices and calibrated as required. Standardised procedures were developed for the performance of the medical assessments (section 5.6.8) and all HSA staff were trained in these procedures (section 5.6.9).

5.6.1 Postal self-administered questionnaire

All participants were asked to complete a self-administered questionnaire (Appendix 4) which was sent to them in the post. The postal questionnaire was used to assess self-reported health outcomes as well as self-reported exposures and experiences. The postal questionnaire sections, and accompanying question numbers and section labels or headings, included:

- A definition of a Gulf War veteran for the purposes of the study and a self-report of the participant's perception of their Gulf War status (Question 1).
- Demographic information *(A. Personal Details. A1-12)*.
- Assessment of self-reported exposures through:
  - History of military service postings *(B. Military Postings. B1-4)*,
  - Gulf War deployment history *(C. Gulf War Deployment. C1-13)*,
  - Active (war or peacekeeping) deployment history *(D. Deployments. D1a-9)*,
  - Stressful military service experiences *(E. Military Service Exposures. E1)*,
  - Civilian occupational history *(F. Civilian Occupational History. F1-4)*.
- Assessment of health outcomes *(G. Health. G1-47)* through:
  - The Short-Form-12 Health Survey (SF-12) *(G1-7)*,
  - The 12 item General Health Questionnaire (GHQ-12) *(G8-19)*,
  - A 63-item symptom questionnaire *(G20. q1-63)*,
  - A 17-item neurological symptom questionnaire *(G20. q64-80)*,
  - A 61-item questionnaire relating to diagnosed or treated medical conditions (*G21-22)*,
  - General medical history *(G23-27)*,
  - Smoking and tobacco consumption *(G28-30)*,
  - The AUDIT questionnaire for alcohol intake and its effects *(G31-40)*,
  - The Posttraumatic Stress Disorder Checklist (PCL-S) *(G41a-41b)*,
  - Self-report of reproductive outcomes and any children with congenital malformations or cancer *(G42-46)*,
  - Self-report of infertility *(G47)*

- Open questions allowing the reporting of additional and important military experiences, exposures or health concerns *(H. Final Questions. H1-3).*
- Confirmation of current contact details *(I. Contact Details).*
- Opportunity to nominate a medical practitioner to receive a copy of their medical report *(J. Nomination of a Medical Practitioner).*

The questionnaire took up to two hours to complete and was undertaken by participants in their own time at home prior to attending for the medical assessment.

5.6.1.1 Demographic information

Participants were asked to provide demographic information in relation to gender, date and country of birth, Aboriginal or Torres Strait Islander origin, language spoken at home, current marital status, any change in marital status since August 1991, highest education qualification completed, current occupational status, any period of unemployment greater than 3 months since August 1991 and current main source of income (A. Personal Details).

5.6.1.2 Exposure assessment

Exposure assessment included Gulf War specific exposures, as well as potential confounding exposures experienced during non-Gulf War military life and civilian occupational life that may also have influenced health outcomes.

Gulf War veterans were asked about medications and immunisations that were administered during the Gulf War deployment.

Participants were asked about chemical and environmental (C & E) exposures, which may have occurred during:

- the Gulf War deployment only, eg SMOIL;
- non-Gulf War active deployments, eg exposure to heat or cold;
- military activities when not on deployment, eg exposure to exhaust fumes; or
- civilian occupational activities, eg exposure to pesticides.

Recall of occupational exposure to specific substances can be unreliable,[252] therefore subjects were asked for details of their military and civilian job histories, such as their job titles.

Participants were asked about psychological stressors specific to military activity (eg coming under enemy attack), that may have occurred during:

- the Gulf War deployment only;
- non-Gulf War military activities, including active deployments other than the Gulf War and other military activities, including training exercises, when not on deployment.

Table 5.1 lists the chemical, environmental, medical and psychological exposures that were investigated by self-report, the corresponding question number of the postal questionnaire and the sources of the questions.

Table 5.1 Table of relevant exposures, question number and sources of the question

Exposure	Question number	Source
Chemical Warfare	D3, D4, C6	Monash, [22]
Respirator Use	D4	Monash, [22]
NBC suit use	D5	Monash, [22]
Pesticide exposed	D2 q7, 8, 19-23. B. F	Monash, [16, 22]

Exposure	Question number	Source
Pesticide user	D2 q7, 8	Monash, [16, 22]
Insect repellent	D6	Monash, [16, 28]
Depleted Uranium	D2 q1, 2. C5, C6, E1 q2	Monash, [22, 28]
SMOIL/D	D2 q10. C4, F	[16, 22, 28]
Dust	D2 q10.	Monash
Infectious agents	D2 q4-7, 17, 18. E1 q6-8. B.	Monash, [16, 22]
Possibly contaminated food	D2. q4, 5. E1 q6	[22]
Possibly contaminated water	D2. q6-9. E1 q6, 7	Monash, [16, 22]
Insects	D2 q17, 18	[16]
Exhaust	D2 q15, B. F	Monash, [16, 22]
Fuel	D2 q7, 9, 12. E1 q6, 7. B. F.	Monash
Solvents	D2 q13. B. F	Monash, [22]
Solvent/skin	D2 q8, 9, 14. E1 q7	[16, 22]
Heat or Cold	E1 q5	Monash, [16]
CARC paint	D2. q3	[16, 28]
Sun screen	D2 q16	Monash
Immunisations	C7-9, 13	[21, 61, 157]
Medications	C10-12, 13	[21]
Post deployment experiences	D9	Study focus group of ADF veterans and personnel, Consultative Forum, Monash, DVA
Psychological stressors	E1 q1-44	Monash, study focus group of ADF veterans and personnel ,[21, 22, 253-255]

Exposure to passive smoking, ionising and non-ionising radiation were not addressed in this study.

Some of the exposure questions were modified to make them more relevant to Australian veterans and to maintain consistency with the style of the rest of the questionnaire. Alterations to the questions were also made on the basis of consultation with a focus group of veterans of a number of deployments held in Melbourne in June 2000, with the Scientific Advisory Committee and Consultative Forum for the study.

5.6.1.2.1 History of military service postings

Participants were asked to specify their service type, the year they joined the ADF, year of departure (unless still serving) and rank achieved on Jan 1991. They were also asked to list any non-reserve postings held for 3 months or more and to report whether they regularly worked with or handled pesticides, solvents, fuels or engine exhaust during such postings.

The military service postings history was used to:

- Subgroup by type of service
- Subgroup by rank

- Identify specific chemical and environmental exposures so that, if necessary, the exposure could be adjusted for in any investigation of a possible association between a health outcome and similar exposures that occurred in the Gulf War.

5.6.1.2.2 Gulf War deployment history and specific exposures

This section of the questionnaire assessed exposures specific to the Gulf War deployment including services with specific Defence Force groups, service in specific locations, exposure to smoke, oil and dust from burning oil wells and exposure to medications and immunisations.

General Gulf War deployment details that were requested included deployment dates, the identity of ship, unit or squadron with which the veteran deployed, the rank held at the time of deployment, primary duties, job title or trade and any service with Operation Habitat.

The general deployment details were used to subgroup members of the Gulf War veteran study group by whether their deployment was completed before the commencement of the air war on 17th January 1991.

Proximity to the ground war and to significant events such as the Camp Doha fire and the demolition of weapons at Khamisiyah was assessed. Subjects were asked to identify the position and timing of any land based activities using maps which were based on those developed for a UK study.[28]

Exposure to smoke and oil and dust (SMOIL) was assessed through self-report of number of days of exposure and number of hours, outside or on upper ship decks, on each of these days.

Exposure to medications and immunisations (referred to as vaccinations in the postal questionnaire) specific to the Gulf War deployment were assessed using questions based on those used by Kings College and Manchester University research groups.[21, 157]

Participants were asked:

- whether they had their World Health Organisation (WHO) yellow vaccination booklet to refer to (C7),
- the number of immunisations they received (C8),
- the timing of these in relation to their deployment and transit to the Gulf (C8),
- the time period over which they received them (C8),
- the individual immunisations that they think they received (C9) (including routine and biological warfare vaccines),
- self-reported significant reactions to immunisations or medications that they received, and an indication of the severity of any such reactions (C13),
- whether they took:
  - anti-nerve agent pills (C10)
  - malaria tablets (C11)
  - anti-biological warfare tablets (C12), and if so, for how long and in what quantities (C10-12).

The difficulty in recalling immunisations received ten years ago was acknowledged, and a number of measures were used to increase or assess the accuracy of recall. These were:

- participants were asked to refer to their WHO yellow vaccination booklets, if available, when completing this section of the postal questionnaire and to bring these with them to their medical assessment so they could be photocopied,

- efforts were made to access policy documents relating to the immunisation schedules for each ship to try and validate participants' immunisation experience where uncertainty existed

Efforts were made to verify self-reported information on the use, and duration of use, of pyridostigmine bromide, antimalarials and anti-biological warfare medications against Australian Defence Force policy documents. However there was likely to be considerable variation in individual compliance with self-administered medication such as pyridostigmine bromide and the study analysis relied primarily on the self-reported exposure data.

A deployment immunisation and medication history was not sought for veterans other than those who were deployed to the Gulf War. A comparison of the background exposure to immunisations and medications for the Gulf War veterans and comparison group was considered in a manner similar to other exposures; that is, through a comparison of other active deployments that were reported and through their duration of military service.

5.6.1.2.3 Active (war or peacekeeping) deployment history and deployment exposures

All participants were asked to indicate whether they had taken part in any active deployments and to identify specific chemical or environmental exposures during those deployments. Gulf War veterans were additionally asked to describe the exposures that took place during the Gulf War.

The participants were provided with a list of active deployments, supplied by the ADF (D1b). The list included war and non-warlike operations, UN peacekeeping and peacemaking operations, service protected evacuations, humanitarian aid operations, humanitarian assistance and was restricted to operations with more than 10 persons that were not security sensitive. Participants were asked to nominate the active deployments they had been on, the year first deployed, the duration of the deployment, and whether they were ordered to serve or volunteered (D1a, b q1-26). Space was provided for participants to nominate additional deployments. Goodwill deployments and training exercises were excluded.

Participants were then asked about chemical and environmental exposures (D2-7) and post deployment experiences (D9) in relation to these active deployments. Participants were asked to indicate whether they were exposed (yes/no) and the extent of exposure (rarely/sometimes/never) to a variety of chemical and environmental exposures. The chemical and environmental exposures of interest are summarised in Table 5.1.

The participants were asked to assess the extent of some exposures during the Gulf War and also during their entire military history (Section E) eg experiences of heat and cold. The participants were asked to assess other exposures during the Gulf War and during other active deployments (Section D) eg to locally sourced/non-military food. In addition, participants were asked to identify the pesticides that they used or were exposed to, the chemical warfare agents that they believed that they had been exposed to, the frequency that they used chemical protective clothing and respirators, and the reasons why they used this protective equipment.

A 17-item Post Deployment Experiences questionnaire (D9. q1-17) was developed to assess the experiences of veterans upon return from active deployments. The focus group, which was run for the purpose of constructing the Military Service Experience questionnaire (section 5.6.1.2.4) provided input about a variety of post deployment experiences which potentially contributed to a veteran's overall experience of a deployment. Themes explored in the Post Deployment Experiences questionnaire included whether veterans felt recognised

and acknowledged by the ADF, Australian Government and Australian people for their deployment activities, whether they felt adequately debriefed, proud of their activities, improved as a leader, more knowledgeable about world issues and more respectful of other veterans.

5.6.1.2.4 Military Service Experience questionnaire

Psychological stressors were assessed using the Military Service Experience (MSE) questionnaire (E1. q1-44). The MSE questionnaire was a 44-item questionnaire designed by the Monash study team for this study, to measure the occurrence and severity of stressful military service experiences relevant to ADF personnel. Existing research instruments designed to measure military or combat-related stressors, such as the Laufer Combat Scale[253] and the Combat Exposure Scale (CES),[254] were considered not fully relevant to the Australian study population. These instruments focus largely on combat exposure in Army infantry who have experienced direct military attack. The Australian Gulf War veteran population, in contrast, were primarily Navy personnel whose experiences involved threat of military attack but few actual encounters. Similarly, many of the recent active deployments and peacekeeping operations, undertaken by Australian military forces, have involved few direct combat encounters and few casualties. Nonetheless, these deployments often involved high risk of military attack including threat of nuclear, biological and chemical warfare, extreme environmental conditions and, often, social isolation and poor organisational conditions. Therefore the MSE questionnaire was designed to explore the severity of stress associated specifically with Australian military experiences. Both war-like deployments and training or other routine military activities were included in the circumstances under which these experiences may have occurred, as it has been during training exercises and routine deployments that the Australian military have encountered several of their most severe accidents in recent times. These include the Black Hawk helicopter accident in June 1996, in which 18 ADF personnel died and a further 12 were injured,[256] and the accidental fire on HMAS Westralia in May 1998 which resulted in a further four deaths.[257]

In developing the MSE questionnaire, existing questionnaires measuring combat severity were searched for items deemed relevant to the Australian military experience. Instruments included in the search were the Laufer Combat Scale, modified for studies of United States military personnel involved in Operation Desert Storm,[253] the CES[254] and the War Zone Stress Exposure Scale (WZ-SES).[255] Also included in the search were the exposure questionnaire items used by the Kings College research team in their Gulf War veteran research.[21] Many of these items were subsequently used in the Health Study of Canadian Forces Personnel Involved in the 1991 Conflict in the Gulf.[22] In addition to items drawn from previously used instruments, several new items were constructed, based on information about known Australian military experiences including accidents and anecdotal evidence provided by veterans of the Gulf War and other deployments.

A total pool of 76 possible items was collated covering experiences such as military attack, threat of chemical warfare, lack of preparation, fear of death, responsibility for the lives of others, physical discomfort, risk of disease, accidents causing death or injury, social isolation and poor unit cohesion.

The 76 items were subsequently circulated to a focus group of ten male and two female Australian former, or current, ADF personnel. This group included veterans of the Gulf War, veterans of other deployments and some personnel who had not been deployed. The focus group participants were invited to:

1. List any additional key experiences which were missing from the list and which they considered to be important stressors relevant to Australian military activity.
2. Strike out any listed experiences which they considered NOT important or relevant to Australian military activity.
3. Indicate, in order of severity, the ten listed items which they considered the most important stressors relevant to Australian military activity.
4. Indicate the ten listed items which they considered the least important stressors relevant to Australian military activity.

Focus group participants were then invited to meet as a group with Monash study team members and representatives of DVA and the Australian Centre for Posttraumatic Mental Health. Discussions centred on stressful military activities that were most relevant to members of the group. Some new issues, such as experiences of sexual harassment, were tabled during the focus group discussions and some events considered irrelevant or trivial, such as 'falling overboard', were removed from the lists.

Subsequent to the focus group discussions the Monash study team pared the original 76-item pool to a final 44 items, which comprised the MSE questionnaire and which were included in the postal questionnaire.

5.6.1.2.5 Civilian occupational history

Participants were asked to state whether they had ever been members of the Country Fire Authority and to list civilian jobs held for more than 6 months including duration, job title, industry sector and company/employer for each job. They were also asked for each job to assess their exposure to pesticides, fuels, engine exhaust, solvents, infectious diseases and trauma. If they used pesticides in any of these jobs, they were asked to list them and describe what they used them for. We asked about exposure to specific chemical and environmental hazards so that if necessary, the exposure could be adjusted for in any investigation of a possible association between a health outcome and similar exposures that occurred in the Gulf War.

5.6.1.3 Health outcomes assessment

Health outcomes assessment included assessment of participant's physical and psychological health through data collected in both the postal questionnaire and the HSA medical assessment. The following sections describe the health outcome measures that were included in the postal questionnaire.

5.6.1.3.1 Short-Form-12 Health Survey (SF-12)

The Short-Form-12 Health Survey (SF-12) (G1-7) is a self-administered generic measure of health status.[258] It was developed to be a brief, yet valid, alternative to the longer SF-36[259] for use in large surveys of general and specific populations as well as large longitudinal studies of health outcomes. It has become one of the most widely used instruments for monitoring the health of populations,[258] and was included in the Australian National Survey of Mental Health and Wellbeing of Adults.[260]

The instrument's twelve questions explore eight concepts commonly represented in health surveys, namely physical functioning, role limitations due to physical problems, bodily pain, general health, energy and fatigue, social functioning, role limitations due to emotional problems, mental health and change in health. Responses are differentially weighted and combined to produce a 'Physical Component Summary' (PCS-12) score between 0 and 100

as an indicator of physical health, and a Mental Component Summary' (MCS-12) score between 0 and 100 as an indicator of mental health

Both the PCS-12 and the MCS-12 use the same 12 items but different weights. These weights were constructed by the developers of the SF-12 to produce PCS-12 and MCS-12 scores that would have a mean of 50 and a standard deviation of 10, if applied to the US general population.[258] US population norms are used to allow results to be compared with other studies. The higher the score, the better the physical or mental health status. The items in the scale refer to the four weeks prior to the completion of the questionnaire. Responses to all 12 items are required for summary scores to be derived.

Whilst not quite displaying validity as high as the SF-36, the SF-12 is believed to represent a very satisfactory trade-off between reduced questionnaire length and reduced precision for large study groups.[258] Test-retest reliability for the PCS-12 scale has been found to be 0.89 in a US general population survey[261] and 0.86 in a UK general population survey.[262] Reliability coefficients of 0.76 and 0.77 were found for the MCS-12 scale in the US and UK studies respectively. Observed PCS and MCS scores, using the SF-12, can be reliably compared with those observed in studies using the SF-36, with both instruments shown to reach similar statistical conclusions about group differences.[263]

5.6.1.3.2 Twelve item General Health Questionnaire (GHQ-12)

The GHQ-12 (G8-19) is a twelve item, abbreviated version of the 60-item General Health Questionnaire.[218] It is a brief, self-administered screening instrument designed to detect current, diagnosable psychiatric disorders in general population surveys, primary medical care settings or among general medical outpatients. The instrument covers four identifiable elements of distress; those being depression, anxiety, social impairment and hypochondriasis. The instrument is not intended to distinguish among psychiatric disorders or to be used in making a diagnosis of an actual disorder. Emphasis is on changes in condition, not on absolute level of a problem, so items compare the present state to the person's normal situation.

Studies have found that the scale shows consistently high reliability and validity measures.[218, 264] Split half reliability on the 12-item version has been reported at 0.83[218] with Cronbach's coefficient alphas[265, 266] ranging from 0.82 to 0.90.[267] Sensitivity and specificity ranges are reported between 74.2% and 95.0%.[218]

The GHQ-12 was used by the King's College Gulf War Illness Research Unit in their study of 4248 Gulf War veterans.[21] This instrument was also used in the Australian National Survey of Mental Health and Wellbeing of Adults.[260]

There are three commonly employed methods of scoring the GHQ-12.[268, 269] The standard method[218] involves coding the four possible responses to each question as 0 – 0 – 1 – 1 and then summing the binary scores, giving a total score ranging from a minimum of 0 to a maximum of 12. Another method of scoring, generally known as the Likert method, makes use of a four point scale, coded 0 – 1 – 2 – 3. When these values are summed a total score ranging from 0 to 36 is obtained.[218] Another scoring method, known as the Chronic method,[270] proceeds in the same manner as the standard method except that responses to negative items such as 'Have you recently lost much sleep over worry?' are coded 0 – 1 – 1 – 1. The latter approach assumes that the response 'no more than usual', which would otherwise be coded as 0 (good health) using the standard method, is indicative of the presence of a chronic problem, and so would be coded as 1. For all three scoring methods, higher scores indicate an increased likelihood of psychological ill-health. A variety of thresholds or

cut-off scores for determining caseness, or possible psychiatric condition, have also been employed with the GHQ-12.[264, 268, 271]

The scoring method for the GHQ-12 in this study, and determination of the most appropriate GHQ-12 caseness score, is described in chapter 11.

5.6.1.3.3 Symptom questionnaire

The 63-item self-report symptom questionnaire included respiratory, cardiovascular, musculoskeletal, dermatological, gastrointestinal, genitourinary, neurological, neuropsychological or cognitive, and psychological symptoms (G20. q1-63). It was based on the symptom questionnaire developed and used by the King's College Gulf War Illness Research Unit,[21] which was based on the Hopkins Symptom Checklist,[272] and employed the same severity scale for symptoms reported to have occurred in the last month. It also included some symptoms used in other overseas symptom prevalence surveys. Similar symptom questionnaires and symptoms have been used in a number of overseas postal surveys investigating the health of their country's Gulf War veterans.[16, 20-22, 73, 157, 158, 162] Such symptom questionnaires have also formed the basis for subsequent factor analyses by these research groups.[73, 154, 157, 158, 160] The neuropsychological symptoms in the symptom questionnaire were similar to those used to evaluate and compare neuropsychological function between the study groups in previous Gulf War studies.[16, 21, 28, 31, 73, 154, 157, 158, 160, 163]

In addition to enabling internal comparisons of self-reported symptoms within the study groups, the use of the symptom questionnaire allows comparisons to be made with the results of overseas studies. The symptom questionnaire also formed the basis for the factor analyses of symptoms in chapter 18. Participants were asked about the occurrence of symptoms in the past month, and, if symptoms were experienced, the severity of those symptoms according to whether they were 'mild', 'moderate' or 'severe'.

5.6.1.3.4 Neuropathic symptom questionnaire

The 17-item neuropathic symptom questionnaire asked about neuropathic symptoms indicative of peripheral neuropathy experienced in the past month (G20. q64-80). The instrument was developed in consultation with a neurologist specifically for this study, as a suitable pre-existing instrument could not be identified. The questions were based on those included in other studies of neurological function[273, 274] and related to four parameters of peripheral neurological dysfunction:

- muscle weakness
- sensory disturbance
- autonomic function, and
- severity of neurological dysfunction.

5.6.1.3.5 Doctor diagnosed or treated medical conditions

This 61-item medical conditions questionnaire asked about medical problems or conditions that had been diagnosed or treated by a doctor (G21.q1-61). Subjects were also given the opportunity to list additional medical conditions that had been diagnosed or treated by a doctor (G22). The term 'medical doctor' was used to qualify the person who diagnosed or treated the problem or condition in order to standardise the reference point and context for that diagnosis or treatment. This questionnaire was based on the medical conditions questionnaire developed and used by the King's College Gulf War Illness Research Unit[21] as well as including several conditions considered relevant to Australian veterans. As was the case with the symptom questionnaire (section 5.6.1.3.3), similar medical conditions questionnaires have been used in a number of overseas postal surveys investigating the health

of Gulf War veterans.[16, 20-22, 73, 157, 158, 162] In addition to enabling internal comparisons of self-reported medical conditions within the study groups, the use of the medical conditions questionnaire allows comparisons to be made with the results of overseas studies.

Subjects who answered 'Yes' to a medical condition were asked to identify the year in which the condition was first diagnosed, and whether the medical condition had been treated by a doctor in the past year. These two sub-questions served to locate the diagnosis temporally in relation to the Gulf War and to give an indication of the current status of that condition.

5.6.1.3.6 General medical history

Hospitalisation

The questions relating to hospitalisation (G. 23) were based on those used in a study of US Gulf War veterans.[20] Participants were asked whether they had been hospitalised overnight or longer because of illness or injury during the past 12 months, and if so, what was the duration of, and reason for, the hospitalisation.

Functional impairment due to illness or injury

The questions relating to functional impairment due to illness or injury (G. 24) were also based on those used in a study of US Gulf War veterans.[20] Participants were asked whether they had stayed in bed or at home all or part of any day because they did not feel well or as a result of illness or injury in the past two weeks.

Current use of medication

Participants were asked about current use of medicine including tablets, creams, inhalers or other drugs (G. 26). Medications were coded using an electronic version of the Monthly Index of Medical Specialties (MIMS).

Family history

Participants were asked whether they had a family history of asthma, stroke when less than 65 years of age, a heart attack when less than 65 years of age, diabetes and cancer. Responses were coded according to the ICD-9 classification system.[275]

5.6.1.3.7 Cigarette smoking and tobacco use

Exposure to cigarette and tobacco smoke was assessed with a brief set of questions (G28-G30) designed to determine:

1. Status of current, former or never/occasional smoker
2. Age started (for current and former smokers)
3. Age stopped (for former smokers)
4. Pack years of cigarette consumption based on an estimated average number of cigarettes smoked per day, grams of tobacco smoked per day (not including from cigarettes or cigars) and cigars smoked per week, and duration of smoking in years between the age started and the age stopped as given by the participant.

5.6.1.3.8 Alcohol consumption

The Alcohol Use Disorders Identification Test (AUDIT) Core questionnaire was used to quantify current alcohol use and detect alcohol disorders (G31-40). This scale was developed by WHO-affiliated investigators for the identification of currently active, hazardous and harmful alcohol consumption.[276] The 10-item AUDIT core questionnaire measures alcohol consumption, dependence symptoms and personal and social harm reflective of drinking. Items refer to the previous year and are scored according to their frequency of occurrence

rather than their presence or absence. Studies have shown the internal reliability of the AUDIT to be 0.86.[277]

In addition to the inclusion of the AUDIT in the study postal questionnaire, alcohol disorders were also investigated as part of the psychologist's assessment (see section 5.6.2.2)

5.6.1.3.9 Posttraumatic Stress Disorder Checklist – S (PCL-S)

The Posttraumatic Stress Disorder Checklist (PCL) is an easily administered self-report rating scale for assessing the 17 DSM-IV symptoms of PTSD. First developed in 1993[278] the PCL was normed in part on a Gulf War veteran sample. Diagnostic utility of the PCL was determined by using the PCL scores to predict PTSD diagnosis derived from the Structured Clinical Interview for DSM-III-R (SCID). It has excellent test-retest reliability, over a two to three day period, and internal consistency is very high for each of three groups of items corresponding to the DSM-IV symptom clusters as well as for the full 17-item scale.[278, 279] The PCL correlates strongly with other measures of PTSD such as the Mississippi Scale, the PK scale of the MMP1-2 and the Impact of Events Scale, and correlates moderately with the Combat Exposure Scale.[278-280] Data are available on Australian Vietnam veterans,[281] US peacekeeping forces,[282, 283] US Gulf War veterans[176, 177] and from many civilian studies.[279, 284, 285]

The PCL-S used in this study (G41a-G41b, q1-17) is one of three versions of the PCL available. The PCL-M is a military version with questions that refer to *"a stressful military experience"*. The PCL-C is a general civilian version that is not linked to a specific event. Its questions refer to *"a stressful experience from the past"*. The PCL-S is a non-military version that can be referenced to any specific traumatic event. The PCL-S allows the respondent to nominate the criterion event and subsequent questions refer to *"the stressful experience"*.

In this study a slight modification was made to the PCL-S stem question which originally read "Please consider the event that you found most stressful or upsetting.". The question was changed to read "Please consider the event or group of events, military or non-military, in your life that you found most stressful or upsetting.". The modification was implemented on the basis that:

a) in some cases, a stressful event with the potential to precipitate PTSD could be a group of related events, rather than a single discrete event. For example, there could be several incidents encountered during a combat deployment which combine to precipitate a PTSD reaction.
b) as the primary focus of the study is military related, participants may feel that they are obliged to nominate a stressful military event, or group of events, and fail to consider a stressful civilian event.

5.6.1.3.10 Reproductive health outcomes

The following aspects of reproductive health outcomes were investigated:

- *Self-report of fertility difficulties (G47).*

A short series of questions relating to self-report of infertility, based on those used in a recent fertility study[286] was included in this study (G47).

- *Self-report of pregnancies resulting in miscarriages, stillbirths or a termination of pregnancy (G42-43).*

Participants were asked how many times they had ever been pregnant or fathered a pregnancy, and if any of these pregnancies resulted in a miscarriage, a still birth or a termination of pregnancy.

- *Health outcomes in live born children (G45a, b).*

For live born children, questionnaire respondents were asked to provide information such as date of birth, birth weight and term of gestation and to identify any birth defect or chromosomal abnormality, cancer or other serious health problem. If a child had died respondents were asked to provide the cause and date of death.

- *Validation of reports of children with cancer*

The study consent form included consent for reports of children's cancers to be matched against the records of the national cancer registry. To facilitate this matching process, questionnaire respondents were asked to provide identifying information such as their children's full names and dates of birth.

5.6.1.4 Nomination of a medical practitioner to receive a copy of their medical report

The participants were invited to nominate a medical practitioner for the purposes of sending out a copy of their medical report as prepared by the HSA doctor. Signed consent was required for the release of this information. Participants who did not wish to nominate a medical practitioner were not required to do so.

5.6.2 Medical assessment

All participants were invited to attend for a medical assessment at one of the HSA medical centres. Assessments were conducted at one of HSA's medical centres or by a mobile team dispatched to a more remote area or to a naval base where numbers justified this. Participants were assessed by a medical team comprising a nurse, a clinical psychologist and a medical doctor, all specifically trained for the purposes of the study. Investigations were undertaken using standardised equipment and standardised procedures, in accordance with the protocols and procedures developed by the Monash University study team. Equipment was appropriately calibrated as necessary. Each medical assessment took up to five hours, including breaks for refreshments. The data was recorded at the time of the assessment in a standard Data Collection Booklet that was developed for the study (Appendix 5). A number of measures were instituted to ensure that assessors remained blinded to the Gulf War status of the participant wherever possible. These included instructions to the assessors to refrain from discussing the participant's military service histories. In addition, the sequence of the medical assessment components was carefully tailored to minimise the possibility of any disclosure by the participants of their Gulf War status.

In the following sections describing the medical assessment components, the page numbers in parentheses refers to the page number of the Medical Examination Data Collection Booklet where that component of the assessment was recorded.

5.6.2.1 Nurse-administered data collection

A Registered Nurse conducted the first part of the assessment process. This involved:

- Greeting the study participants and checking their identity; introducing themselves, explaining what would happen in the assessment process and answering questions,
- Obtaining and witnessing informed consent (detachable page),
- Obtaining emergency contact details (reverse of detachable page),
- Standardised measurements of height, weight, hip and waist circumference (p1),

- Standardised measurement of diastolic and systolic blood pressure according to the standard protocol recommended by the British Hypertension Society (p1),
- Standardised assessment of corrected visual acuity using the Snellen Eye Chart (p1),
- Assessment of symptoms of tiredness or fatigue for the purpose of selecting cases and controls for the collection of blood for lymphocyte subsets (p2),
- Collection of blood samples (p2),
- Completion of the interviewer-administered Respiratory Health Questionnaire with the participant (p3-7),
- Performance of skin prick tests to measure atopy (p8),
- Standardised measurement of respiratory function using the Spirocard spirometer according to the American Thoracic Society (ATS) protocol (p8,10),
- Urinalysis for blood, protein, glucose and nitrites (p9),
- Photocopying the WHO yellow vaccination booklets provided by Gulf War veterans (p9,12), and
- Checking returned postal questionnaires for completeness (done last in their examination to help maintain blindness to the participant's Gulf War status),
- Documenting whether they remained blinded to Gulf War status (p9).

The nurses were also trained to take on a case management and quality assurance function, to ensure each participant was managed efficiently through the medical assessment process. The quality assurance function included checking all documentation to ensure it was complete and consistent before transporting it to the Monash University study team.

5.6.2.1.1 Informed Consent

Participants were asked to sign an Informed Consent Statement giving their consent to participate in the study. Participants could participate in all aspects of the study or could indicate on the Informed Consent Statement those aspects of the study in which they did not consent to participate. The purpose of the study and their role in the study was explained in the Explanatory Statement that accompanied the initial invitation to participate. The Explanatory Statement explained the nature and content of the research study, the voluntary nature of participation, what participation in the study involved, possible risks and inconveniences, issues related to the storage of blood, confidentiality and privacy, use of data and data management and participation in possible future investigations. Contact details for the study team, Scientific Advisory Committee and overseeing Ethics Committees were provided so that participants could ask questions or express complaints or concerns about the conduct of the study. Trained HSA nurses obtained and witnessed the informed consent at the commencement of the medical assessment. Consent was also sought, through an Informed Consent Statement sent to them for their signature and return, from participants who completed the postal questionnaire only.

5.6.2.1.2 Standardised measurement of height, weight, hip and waist circumference

- Height was measured in centimetres, to one decimal place using a stadiometer, as the maximum distance from the floor to the vertex of the head with shoes removed (p1).
- Weight was measured in kilograms, to one decimal place, in light clothing and without shoes, using the Tanita Body Composition Analyzers TBF-410 that were dedicated to the study (p1).
- Waist and hip circumferences (p1) were measured using a tape measure according to guidelines described by the National Health and Medical Research Council

(NHMRC).[287] Waist circumference was measured in centimetres, to one decimal place, at the smallest circumference below the rib cage and above the umbilicus taken at the end of normal expiration. Hip circumference was measured, in centimetres to one decimal place, at the largest circumference at the posterior section of the buttocks.

Body mass index

Body mass index (BMI) is a simple index of weight-to-height ratio that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2). It is considered to provide the most useful, although crude, population-level measure of obesity and the risks associated with it. The most recent WHO categories[288] differ slightly to those traditionally recommended for use in the study of Australian populations by the NHMRC.[287] The 1995 National Nutrition Survey adopted the World Health Organization's recommendations for BMI categories, but included split categories of the normal or acceptable weight range to enable comparison with the NHMRC categories.[289] BMI for study participants was calculated using their height and weight measurements. Participants were then classified according to the categories used by the National Nutrition Survey as listed in Table 5.2.

Table 5.2 Classification of adults according to BMI

Classification	BMI kg/m2	Risk of comorbidities
Underweight	<18.50	Low (but risk of other clinical problems increased)
Normal range	18.50-<20.00	Average
	20-<25.00	
Overweight:	≥25.00	
Pre-obese	25.00-<30.00	Increased
Obese class 1	30.00-<35.00	Moderate
Obese class 2	35.00-<40.00	Severe
Obese class 3	≥40.00	Very severe

Waist circumference and waist-to-hip ratio

Waist circumference and waist-to-hip ratio (WHR) are indicators of the amount of fat located predominantly in the abdominal region. WHR was calculated by dividing each participant's waist measurement by their hip measurement. Resulting ratio scores were rounded to one decimal point. Cut-off points that may define increased risk of cardiovascular disease and all-cause mortality range from >1.0 in men and >0.85 in women[288] to >0.9 in men and >0.8 in women.[287, 289-291] This study has used the cut-points of >0.9 in men aged 19 years and over and 0.8 for women aged 19 years and over as those generally adopted in Australia[287] to define those at health risk from having a central fat distribution.

Waist circumferences greater than 94 cm in males and greater than 80 cm in females indicate increased risk of obesity related complications, and waist circumferences greater than 102 cm in males and greater than 88 cm in females indication substantially increased risk of obesity related complications.[288, 292]

5.6.2.1.3 Blood pressure

Blood pressure was measured twice using a mercury sphygmomanometer (p1) according to the British Hypertension Society protocol

(http://w3.abdn.ac.uk/BHS/booklet/proced.htm).[293] Two readings were separated by at least two minutes and averaged to derive a single systolic and diastolic blood pressure reading. Participants were then categorised according to the guidelines provided by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[294] and the Guidelines Subcommittee of the World Health Organization-International Society of Hypertension,[295] as presented in Table 5.3.

Where a participant's systolic and diastolic blood pressure fell into two different categories, the higher category was applied to classify the individual's blood pressure status.[294, 295]

Table 5.3 Blood pressure categories according to systolic and diastolic readings

Category	Systolic (mmHg)		Diastolic (mmHg)
Normal	<130	and	<85
Optimal	<120	and	<80
High-normal	130-139	or	85-89
Hypertension	≥140	or	≥90
Grade 1 hypertension (mild)	140-159	or	90-99
Grade 2 hypertension (moderate)	160-179	or	100-109
Grade 3 hypertension (severe)	≥180	or	≥110
Isolated systolic hypertension	≥140	and	<90

It should be noted that this classification system[294, 295] is based on the average of two or more blood pressure readings at each of 2 or more visits in adults who are not taking any medication and who have no acute illness. These conditions have not been met in this study where it was impractical to measure blood pressure on two different visits, so the classification system has been used as a framework for comparing the study groups rather than for diagnosing hypertension.

5.6.2.1.4 Visual acuity

Corrected visual acuity was assessed for both eyes using the Snellen Chart at a distance of 6 metres. Visual acuity was recorded (p1) as a fraction, with the test distance recorded as the numerator and the last line of letters in which all letters were read correctly was recorded as the denominator, in a standardised manner.[296]

Subjects who were unable to correctly read the 6/6 line using their refractive correction, eg glasses or contact lenses if worn were categorised as having visual impairment. Visual impairment despite correction with glasses or contact lenses suggests that the defect may not be fully refracted by the glasses or contact lenses or due to an explanation other than a refractive error.[297] Visual impairment was considered as part of the neurological assessment of participants.

5.6.2.1.5 Symptoms of tiredness or fatigue

An abbreviated assessment of any symptoms of extreme tiredness or fatigue was undertaken by the nurses for the purpose of selecting 'cases' and 'controls' for the collection of blood for lymphocyte subsets testing (p2). This abbreviated assessment was based on the first two doctor's questions relating to these symptoms in Section 2 of the doctor's examination (p35).

The procedure for the full assessment of symptoms of extreme tiredness or fatigue is described in Section 5.6.2.3.2.

5.6.2.1.6 Spirometry

Spirometry was undertaken using QRS SpiroCard spirometers with Office Medic software (QRS Diagnostic, LLC; Plymouth, Minnesota, USA) according to the standardised procedures recommended by the American Thoracic Society (ATS),[298] and Thoracic Society of Australia & New Zealand.[299]

The SpiroCard spirometer was chosen for use in this study on the basis of its compliance to ATS standards,[300] its portability and simplicity of use, and its measures for infection control. This is a flow-sensing spirometer that uses a pre-calibrated, non-sterile disposable pneumotach. On each day of use, spirometers were calibrated using a 3-litre syringe (or a 1-litre syringe where a 3-litre syringe was not available). Predicted ventilatory function values were drawn from criteria published by Knudson[301] or ECCS (European Community Coal and Steel) criteria if the participant's parameters were outside the Knudson criteria. Correction for Body Temperature and Pressure, Saturated (BTPS) was automated. Race correction factors of 15% for Asian and Black, African participants were applied.

Participants were instructed to avoid, if possible, the use of anti-histamine based medications in the four days prior to their HSA appointment, and to avoid alcohol, caffeine and asthma medications on the day of their appointment. If any of these contraindicated asthma medications were consumed in the prescribed period, this was recorded and the spirometry was still performed. If a participant had smoked a cigarette within the previous hour, spirometry was performed if possible, at a point later in the examination.

Nurses were trained to instruct and supervise participant's performance of spirometry to ATS criteria[298] as summarised below:

- participants were seated for the testing;
- the use of a nose clip was recommended;
- the forced expiratory manoeuvre was performed with maximum effort immediately following a maximum inspiration;
- participants were required to perform a minimum of three technically acceptable blows with acceptability criteria defined as:
  - satisfactory start-of-test,
  - minimum exhalation Forced Vital Capacity (FVC) time of 6 seconds, and
  - end-of-test criteria;
- participants manoeuvres were to meet the ATS criteria for reproducibility with reproducibility criteria defined as:
  - the largest and the second largest FVC must not vary by more than 0.2L, and
  - the largest and the second largest Forced Expiratory Volume in 1 second (FEV_1) must not vary by more than 0.2L;
- participants were to perform up to, but no more than 8 blows (unless the test was terminated on clinical grounds) until three of these were judged to be technically acceptable and the reproducibility criteria were met.

The HSA doctors were also asked to review the spirometry results in providing feedback to the participant and for quality control purposes in monitoring the performance of spirometry.

In addition to spirometry training for HSA doctors and nurses at the commencement of the study, feedback on the performance of spirometry and additional training was provided in April 2001. Subsequent monitoring and individual feedback was provided over the post-training period.

5.6.2.1.7 Skin prick testing for common allergens

Prior to testing, participants' use of antihistamines in the previous four days was recorded (p8). Skin prick testing was used to assess participant's mast cell reaction to four common aero-allergens: cat dander, mixed grasses, house dust mite and mould.

Allergen solutions (Bayer Australia Ltd to March 2001 then Richard Thompson Pty Ltd both of Sydney, New South Wales) used were:

- House dust mite (Standardised Mite DP *Dermataphagoides pteronyssinus* Strength 30 000 AU/ml)
- Grass mix (Grass mix #7, 1:20 w/v)
- Cat dander (Standardised Cat Pelt Acetone Precipitated Strength 10 000 BAU/ml)
- Mould mix (*Alternaria tenuis, Aspergillus fumigatus, Hormodendrum cladosporioides, Penicillium notatum* 1:10 w/v)

A diluent negative control and a histamine positive control were used to detect any false positive or negative reactions. Control solutions were:

- Negative control (preservative 50% glycerin)
- Positive control (Histamine Acid Phosphate in Sodium Chloride 0.9% 1 in 100{10mg/ml})

A drop of each test solution was placed on the skin of the flexor aspect of the forearm unless this area was not suitable for testing, in which case the skin on the upper back was used if it was suitable. A lancet was passed through each drop of solution with its tip gently lifted through a small portion of epidermis. The maximum diameter, and perpendicular diameter, of any resulting positive skin reaction, typically observed as a red weal, was measured in millimetres and the two diameters averaged. The reactions to the positive and negative controls were measured at 10 minutes, and the reaction to the allergens was measured at 15 minutes after the application of the test solution. A positive result for an allergen was one in which the averaged allergen reaction was 3 mm greater than the averaged negative control reaction.[302]

Skin prick testing was not carried out in areas of abnormal skin, for example patches of psoriasis or active eczema. Participants were not tested if:

- They had experienced a previous serious adverse reaction to skin prick testing,
- They had current unstable asthma, such as current wheezing.

5.6.2.1.8 Respiratory Health Questionnaire

A Respiratory Health Questionnaire was administered by the nurse, and was based on questions from two sources. The purpose of this questionnaire was to identify respiratory symptoms such as wheeze, shortness of breath, cough etc and respiratory medical conditions such as asthma, chronic bronchitis and emphysema that were reported by participants. The majority of the questions relating to wheeze and tightness in the chest, shortness of breath, cough and phlegm from the chest, breathing and asthma were drawn from the European Community Respiratory Health Survey (ECRHS).[303] The questions relating to chronic bronchitis and emphysema were drawn from the American Thoracic Society questionnaire.[304] Both these measures have been used to assess respiratory symptoms and

health in epidemiological studies in adults as well as in studies that combine assessment through a postal survey questionnaire with a clinical examination.

5.6.2.1.9 Laboratory investigations and pathology service

Laboratory investigations

Several blood samples were collected routinely for the purpose of assessing the presence of haematological, biochemical and serological parameters that are indicative of anaemia or inflammation, renal or liver disease, a raised blood glucose or prior exposure to viral infections. One sample, for lymphocyte subset testing in relation to a history of tiredness or fatigue, was collected on a subset of participants only. Samples were also collected for storage and possible subsequent testing. If a participant did not consent to have blood or storage samples collected, they indicated this on the consent form, and the nurse was instructed not to collect such samples.

The laboratory investigations that were performed on all participants are outlined in Table 5.4. The specific investigations were chosen for a number of reasons, including:

- *Investigating or excluding serious infections/inflammation; or significant haematological, liver or renal disease*. Investigations such as Erythrocyte Sedimentation Rate and C-Reactive Protein are routine investigations used in clinical practice to assess patients with a serious underlying disease. If the tests are normal, this suggests that any significant illness, eg advanced malignancy is unlikely. If these investigations are abnormal, it is likely that there is an active infective/inflammatory process involved. When these investigations are abnormal, individuals would usually require further investigation. A Complete Blood Examination, Liver Function Tests, renal function tests (Urea and Creatinine) and urinalysis were used to identify the possibility of significant haematological, liver or renal disease.
- *Investigating or excluding commoner infective causes for chronic health problems.* Tests in this category included IgG against Epstein-Barr virus (IgG EBV), IgG Cytomegalovirus (IgG CMV) and hepatitis C core antibody. Hepatitis B can cause chronic infection and ill-health, but it was decided not to test for hepatitis B core antibody because all Defence Force personnel had been immunised by the time of the Gulf War.

A further blood sample was collected on a subset of participants for the purpose of characterising study participants with chronic fatigue syndrome through an investigation of the characteristics and distribution of lymphocyte subsets. A number of lymphocyte subsets have been associated with chronic fatigue syndrome. These are usually not useful for investigating individual patients because there is significant overlap between those with chronic fatigue syndrome and those without it. Therefore, these tests/markers are used to characterise study groups. The specific lymphocyte subsets that were performed and the procedure for selecting the subset of participants are described in the context of the investigation of chronic fatigue in section 5.6.2.3.2.

Storage of samples for later analysis (overview)

We collected and stored a number of different specimens for possible later analysis. The samples of all types of blood and serum that were collected and stored are outlined in Table 5.5. Some specimens were collected for possible analysis within 12 months of the study, and a serum sample was collected for indefinite storage for possible analysis in the future.

Table 5.4 Laboratory investigations performed on all consenting participants

Haematological tests
• Complete Blood Examination (CBE) – haemoglobin (Hb), red cell count (RCC), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width, total white cell count (WCC) and white cell differential counts and percentages (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets
• Erythrocyte Sedimentation Rate (ESR)
Biochemical Analyses
• Urea and Electrolytes (U&Es) - sodium, potassium, chloride, bicarbonate, anion gap, urea and creatinine.
• Serum calcium and phosphate - total calcium, ionised calcium and phosphate
• Liver Function Tests (LFTs) - total protein, albumin, globulin, total bilirubin, gamma-glutamyl-transferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LD)
• Random plasma glucose
• C-reactive protein (CRP)
Serology tests
• Epstein-Barr virus antibody test (EBV IgG)
• Cytomegalovirus antibody test (CMV IgG)
• Hepatitis C serology (Hep C core Ab)

Table 5.5 Routine storage specimens

Short-term storage of serum for 1 year at -70°C
Buffy coat and plasma storage for 1 year at -70°C
Short-term storage of blood for 1 year at -70ºC, and
Long-term storage of serum for up to 10 years at –70°C.

Storage of samples for possible analysis within 12 months

These included blood, serum, plasma and buffy coat preparations. The specific storage samples were chosen for a number of reasons that are outlined below, including:

- Possible testing within 12 months of a subset of participants based on the health outcomes identified in the study. In the development of the study protocol, it was considered that it may be appropriate and cost-efficient to do some investigations such as Thyroid Stimulating Hormone only on the subset of participants identified with symptoms of chronic fatigue. Symptoms of chronic fatigue syndrome can mimic hypothyroidism, and hypothyroidism should be considered before the diagnosis of chronic fatigue syndrome can be made.[305] Thyroid Stimulating Hormone (TSH) is an appropriate screening test that could be followed up with other Thyroid Function Tests if required.
- A buffy coat sample was collected and stored to enable testing for the presence of *Mycoplasma* organisms in the future. Nicholson *et al* (1996) have demonstrated that DNA from *Mycoplasma* organisms can be detected in some people with Gulf War related illnesses.[223] This organism has been associated with rare but severe disease in normal

hosts and in those with AIDS. As with TSH, it was considered that it may be important to be able to test for this organism as an explanation for chronic fatigue syndrome.

Indefinite storage of a serum sample
Concerns expressed by the Consultative Forum regarding the long-term storage of blood, and thus DNA, were addressed by only storing serum on a long-term basis. These serum samples may only be used for serological and antibody testing but not DNA testing.

As the national pathology service provider for the study, the Institute of Medical and Veterinary Science (IMVS) was responsible for the storage of samples through their contract with DVA.

Pathology service
Early in the study, the laboratory investigations for 18 study participants were performed by Dorevitch Pathology (also a NATA and RCPA Registered Laboratory) in Melbourne.

To standardise pathology testing in this national study a single pathology service, IMVS, located in Adelaide, South Australia undertook the blood testing. Medvet Science, the commercial branch of IMVS, coordinated the sample transportation, liaised with local pathology services in each state and territory involved in the initial handling of blood specimens, and liaised with the local and national courier services responsible for transporting the specimens from HSA offices to these local pathology services and then interstate to Adelaide.

IMVS is enrolled in The Royal College of Pathologists of Australasia (RCPA)/ Australasian Association of Clinical Biochemists (AACB) Quality Assurance Program. It is accredited with the National Association of Testing Authorities (NATA) and operates a Quality Management System that complies with the requirements of AS/NZS ISO 9002. Dr Krystyna Rowland, Specialist Pathologist and Head, Diagnostic Services Laboratory coordinated the role of IMVS in the study.

The testing methodology and reference intervals used by the IMVS are detailed in appendix 6

5.6.2.1.10 Urinalysis
A urine specimen was collected and tested for the presence or absence of glucose, protein, blood and nitrites by a HSA nurse using the N-Neostix Bayer Multiple Reagent Strips for Urinalysis: #2825 according to the manufacturer's instructions (p9).

5.6.2.2 Psychologist's assessment
Upon completion of his or her assessment with the nurse, each participant undertook an interview with a trained HSA clinical psychologist. The interview took, on average, one hour to complete. Questions were drawn from the Composite International Diagnostic Interview (CIDI) Core version 2.1[306] and the Australian Bureau of Statistics 1997 National Survey of Mental Health and Wellbeing.[260] The CIDI involved a set of interviewer-administered questions for which responses were directly entered, by the interviewer, into a computer program. Some additional questions drawn from the CIDI, plus some questions drawn from the 1997 National Survey of Mental Health and Wellbeing, were paper-based but also interviewer administered. The interview was designed to cover a range of affective (depressive), anxiety and substance use disorders.

The psychological health assessment was designed to detect the probable presence or absence of a variety of psychological disorders, but not to deliver a comprehensive clinical diagnosis

for any one condition. The primary instrument of use, the CIDI, is a structured interview designed for research purposes. The complete CIDI comprises 11 structured questionnaire modules which, when scored, report whether diagnostic criteria have been satisfied according to the definitions and criteria of the 10th revision of the International Classification of Diseases ICD-10[307] and the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV.[308]

5.6.2.2.1 Psychological assessment procedure

For this study, seven of the CIDI questionnaire modules were administered to generate a DSM-IV based categorical result, with onset and recency codes, for the following psychological disorders (p13):

1. Somatoform and Dissociative Disorders including:
   - Somatoform pain disorder,
   - Somatisation disorder,
   - Conversion disorder, and
   - Hypochondriasis
2. Anxiety disorders including:
   - Obsessive-compulsive disorder
   - Generalised anxiety disorder
   - Posttraumatic stress disorder
   - Specific phobia,
   - Social phobia, and
   - Agora phobia and Panic disorder
2. Depressive disorders and dysthymic disorders
3. Manic and Bipolar Affective disorders
4. Alcohol use disorders
5. Psychoactive substance use disorders.

The psychological health assessment also covered:

- Eating Disorders (p22)

The complete CIDI questionnaire Eating Disorders module was not administered in the interview as this disorder was considered to be extremely rare in the study population and that the focus of the psychologist's assessment should be on aspects of psychological health most relevant to the study population. However, some assessment of eating disorders was considered important as the presence of this disorder can be an explanation for chronic fatigue in some individuals. Therefore to facilitate the study's thorough assessment of chronic fatigue in the study population, five stem questions from the CIDI module were used as screening questions for this disorder. These included those opening questions for which a set of Yes (positive) responses typically lead to the administration of the remaining 12 module questions. These questions were paper-based and administered by the interviewer.

- Schizophrenia and Psychoses (p23)

The CIDI questionnaire module for schizophrenia and psychoses was excluded from the psychologist's assessment on the basis that it was reported to produce excessive false positive diagnoses in an Australian community sample.[309] However, four paper-based screening questions, for schizophrenia and other psychotic disorders, were used in preference to the CIDI module. These questions were drawn from the National Survey of Mental Health and

Wellbeing[260] and were administered by the psychologist. As with eating disorders, psychotic disorders can be an explanation for chronic fatigue and these screening questions were used for the purpose of the chronic fatigue assessment.

Two remaining CIDI modules were not administered:

- Dementia, amnestic and other cognitive disorders. This module was considered of least relevance to the study population.
- Nicotine Use Disorder. Questions pertaining to quantitative use of nicotine, in cigarettes, cigars and pipes, were instead included in the postal questionnaire (section 5.6.1.3.7).

5.6.2.2.2 Modifications to the posttraumatic stress disorder module

The introduction to the PTSD module in the CIDI was slightly modified for the purpose of this study. Typically respondents to the CIDI interview are invited to view a standard list of eleven broad experiences. A participant must have encountered one or more of those experiences to be eligible for a PTSD diagnoses and to continue with the PTSD questions within the module. Item 1 on the list originally read "Have you ever had ***direct combat experience in a war?"*** It was felt that many ADF personnel, who had served on active, operational deployments such as the Gulf War deployment, would not consider that their service included 'direct combat experience' as there were few on this deployment who came under direct military attack. Thus a broader question was devised to ensure inclusion, in this module, of all ADF personnel who served on war-like or peacekeeping operations. Item 1 on the list was therefore altered to read "Have you ever been ***deployed to a war zone or peace keeping operation?****"*

5.6.2.3 Medical examination

The medical examination was conducted by a doctor, trained for the study, as the third component of the medical assessment. Wherever possible the doctor conducting the examination was blinded to the status of the individual as a Gulf War veteran or comparison group subject. The following steps were taken to maximise this:

- Subjects and doctors were advised prior to the examination not to discuss deployment status.
- The doctors were instructed to not view the military service and deployment sections of the postal questionnaire.
- The physical examination was conducted prior to any further assessment of health status or history. This also allowed the doctor not to be influenced by the self-report of symptoms or medical conditions.

In addition to collecting data in a standardised manner for analysis in the study, the doctor also provided the participants with an opportunity to discuss their health and medical concerns, have their health assessed, and receive feedback in the form of a medical report which could be forwarded to the nominated medical practitioners.

In the process of the medical examination, the doctors:

- introduced and explained this section of the medical examination to the participant,
- conducted a standardised physical examination,
- completed the clinician administered "Symptoms of Tiredness or Fatigue" questionnaire relating to a history of extreme tiredness or fatigue and associated symptoms,
- reviewed the self-reported medical conditions section of the postal questionnaire, and asked further questions to assess the likelihood of the diagnosis for each self-reported medical condition according to a predetermined set of criteria,

- asked an open question(s) about the participant's general health and health concerns and re-examined the participant, if necessary, without altering their previously recorded findings,
- supervised and recorded the performance of a short standardised fitness test,
- provided immediate feedback on urgent and/or serious conditions directly to the participant and a letter for them to take to their medical practitioner, and
- completed a medical report, upon receipt of the blood test results, that was sent to the participant, and to their nominated medical practitioner if the participant agreed to this.

5.6.2.3.1 Physical examination

The doctor conducted a systematic physical examination in accordance with the Physical Examination Procedure in the Manual III: Participant Assessment Procedures and recorded his/her findings on the Data Collection Booklet before proceeding with the remainder of the examination.

The physical examination concentrated on the respiratory, neurological and musculoskeletal systems and skin; but also included an examination of the thyroid gland, lymph nodes, and gastrointestinal and cardiovascular systems. Physical examination was bilateral and involved both upper and lower extremities. The format for recording the physical examination findings was based on the case report forms used in the physical examinations as Phase 111 of the US Veterans Affairs National Health Survey of Gulf War Era Veterans and their Families[20, 310] (p25-34). The physical examination components are discussed here in the order they were undertaken during the physical examination:

- thyroid gland was examined for size, tenderness and nodules (p25)
- cardiovascular examination included examination of the radial pulse, heart and peripheral circulation (p25)
- respiratory system examination included examination of the upper respiratory tract, respiratory rate and chest (p26)
- skin and nails were examined for skin rashes (particularly rashes suggestive of inflammatory dermatitis or eczema, psoriasis, skin infections or acne), skin lesion(s) suggestive of skin cancer(s) and solar keratoses (site and description or number), appearance of finger nails and toe nails and presence of tattoos (p26-27)
- gastrointestinal examination included examination of the mouth, abdominal wall, individual organs (liver, spleen, kidneys), abdominal masses, and hernial orifices through cough impulse in the standing position (p27-28)
- epitrochlear, cervical, supraclavicular, axillary and inguinal lymph nodes were examined (p28)
- musculoskeletal examination included examination of the spine (cervical, thoracic and lumbar spine), upper limb joints (shoulder, elbow, wrist, thumb, and fingers), lower limb joints (hips, knees, and ankles), straight leg raising, and muscular or tendon abnormalities (p28-29).
- neurological examination (p29-34) included examination of the cranial nerves; ascertainment of handedness; inspection for muscle wasting (absent, generalised or localised); fasciculations (absent, generalised or localised) or tremor (absent, tremor at rest or otherwise); muscle tone (normal, increased, decreased); power (recorded on the Medical Research Council (MRC) scale of 5-0 where 5 is normal and 0 is no movement); reflexes (biceps, triceps, brachioradialis, quadriceps, and ankle recorded as normal, reduced, absent or increased and plantar reflexes recorded as downgoing, upgoing or

equivocal); coordination (finger-nose test and heel-shin test recorded as normal or abnormal); sensation {vibration sense of tip of the index finger and tip of big toe, and tested more proximally if these locations were abnormal (normal or decreased); position sense tested in distal joint of index finger and big toe (normal or decreased); pinprick sensation tested on thumb, little finger, nipple level, umbilicus, big and little toes (normal, decreased, absent or hyperpathic); station and gait, ie Romberg's test (negative or positive), tandem gait (normal or abnormal), walk on heels and walk on toes (normal or abnormal), arise from a squatting position without the use of arms (yes or no)}.

If the doctors detected an abnormality that was not specifically referred to in the Physical Examination procedure or in the Physical Examination section of the Data Collection Booklet, they were to undertake a more complete physical examination that enabled them to assess this finding and to record this information under the relevant system or in the space for General Comments (p34).

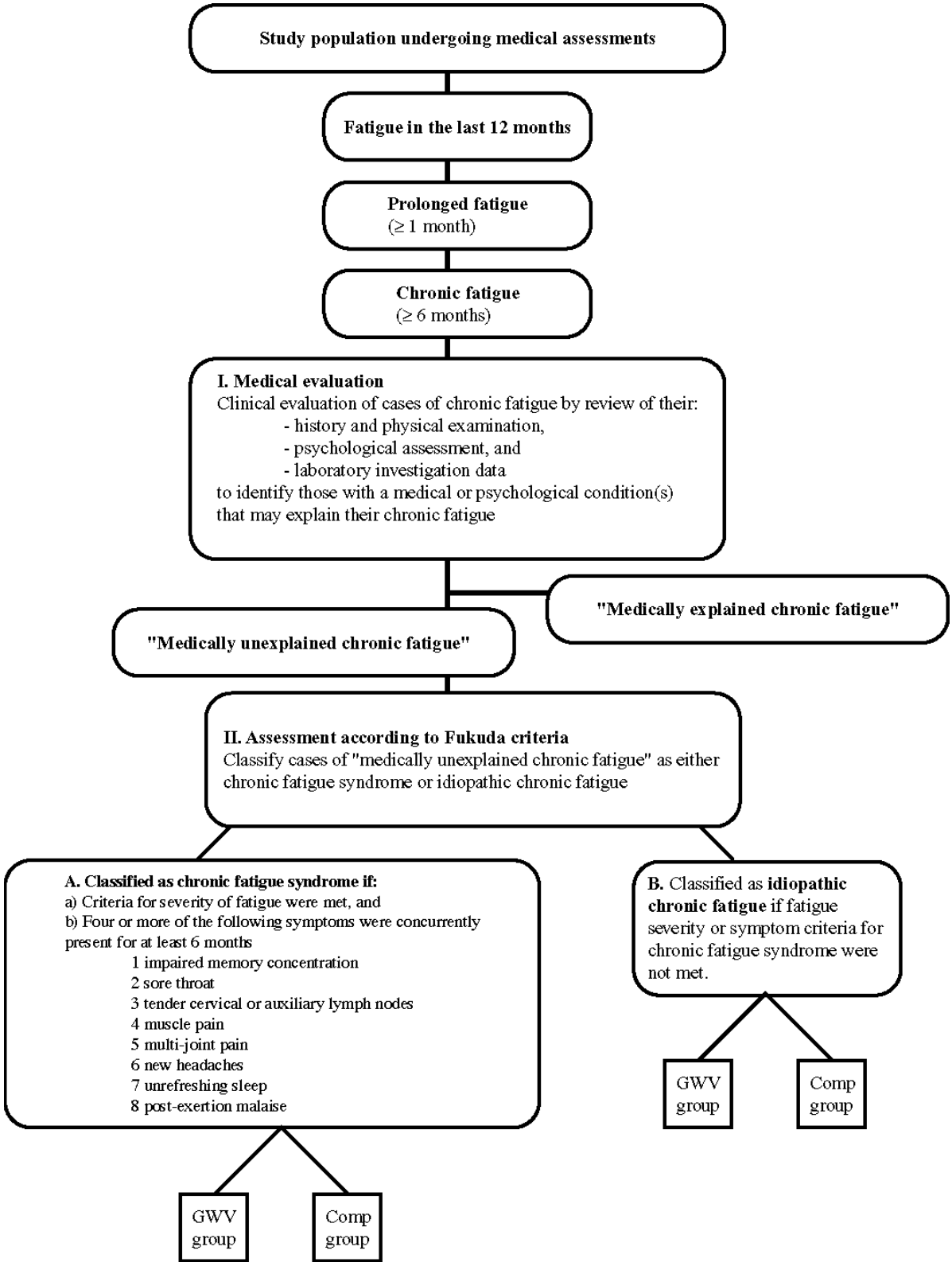
5.6.2.3.2 Assessment of symptoms of extreme tiredness or fatigue

The methodological approach to the assessment of chronic fatigue in this study was based on the criteria for the epidemiological investigation of chronic fatigue syndrome as recommended by Fukuda *et al*.[305] The nature of this condition, criteria for diagnosis and approaches to the epidemiological study of chronic fatigue and chronic fatigue syndrome was also discussed with the Centers for Disease Control and Prevention (CDC) researchers (CDC, personal communication, May 2000), the Iowa group[16, 160] and Australian researchers (Prince Henry Hospital and University of New South Wales researchers, Sydney, Australia, personal communication, May 2000). The approach used in this study was intended to allow a descriptive analysis of the symptomatology and nature of chronic fatigue reported by participants, as well as to consider these cases of chronic fatigue syndrome according to the formal criteria of Fukuda *et al*.[305]

The HSA doctor assessed symptoms of extreme tiredness or fatigue, the duration of such symptoms and the characteristics and severity of this extreme tiredness and fatigue in a structured clinical interview through the 'Symptoms of tiredness or fatigue' questionnaire (p35-37).

The process for defining cases of chronic fatigue syndrome is summarised in Figure 5.1, and this process and the definitions for these fatigue-related health outcomes are detailed in the Chronic Fatigue Syndrome chapter.

Figure 5.1 Process for defining cases of chronic fatigue syndrome.



Lymphocyte subsets

A nested case control study design was developed to assess the immunological profile of participants with chronic fatigue syndrome. Symptoms of extreme tiredness or fatigue were initially assessed by the nurses through the administration of three stem questions (p2) based on the first two doctor's questions relating to these symptoms (p35). The participant's responses were used to select 'cases' and 'controls' for the collection of blood for lymphocyte subsets in addition to routine blood tests, and this was recorded on a Log Sheet for Symptoms of Tiredness or Fatigue kept in each HSA office. A participant was considered:

- a 'case' for the purposes of lymphocyte subset testing if in the past 12 months they had felt extremely tired or fatigued following their normal activities every day, or almost every day, for one month or longer, ie 'Yes' to 'Symptoms of tiredness or fatigue' Q1 and Q2 (p2) or
- a 'control' for the purposes of lymphocyte subset testing if in the past 12 months they had not experienced extreme tiredness or fatigue following their normal activities and they had never been diagnosed with, or treated for, chronic fatigue syndrome by a medical doctor, ie 'No' to both 'Symptoms of tiredness or fatigue' Q1 and Q3 (p2) (and if there was a 'case' recorded on the Log Sheet for Symptoms of Tiredness or Fatigue who did not have a corresponding control).

This selection process was instituted to allow blood to be collected early in the medical assessment, and therefore meet the national pathology courier service requirements.

Lymphocytes can be categorised as T lymphocytes, B lymphocytes or Natural Killer Cells. Immunologists differentiate T and B lymphocytes by characteristic antigens or "surface markers" on their cell membranes, and these antigens are called CD1, CD2, CD3 etc where CD stands for "Cluster of Differentiation". The specific lymphocyte subsets which were tested on the 'cases' and 'controls' were consistent with those performed in other studies of immune function and chronic fatigue in Gulf War veterans[169, 311] and with a general immunodeficiency screen, and are identified in Table 5.6.

Table 5.6 Lymphocyte subsets

Lymphocyte subsets
T cell markers – CD3+, CD4+CD3+, CD8+CD3+, CD4/CD8 ratio
B cell markers – CD19
Natural Killer Cell markers - CD16+CD3-, CD56+CD3-, CD16+/CD56+,CD3-

5.6.2.3.3 Review of the doctor diagnosed or treated medical conditions section of the postal questionnaire

The doctors were asked to check the self-report of doctor diagnosed or treated medical conditions in the postal questionnaire (G21 and G22), for completeness of information with respect to year of onset and recency of treatment. The doctor then asked further questions about each self-reported medical problem or condition to determine whether it was diagnosed or treated by a medical doctor; and if it was, assess the likelihood of the diagnosis. The doctors were not expected to take a full clinical history, rather to ask a maximum of 3 – 4 questions in relation to each medical problem or condition. Doctors then classified each self-reported medical condition according to the following criteria, and recorded this numerical

code in the 'office use only' column on the right hand side of the G21 or G22 table on the postal questionnaire.

> '1' 'Non-medical diagnosis'. The self-reported condition was not diagnosed or treated by a medical doctor.
>
> '2' 'Unlikely diagnosis'. The condition was mentioned by a doctor, perhaps as a possible diagnosis, but the person's history of the condition was not consistent with the diagnosis, and/or the diagnosis was not confirmed by investigation by the treating doctor and treatment was not required.
>
> '3' 'Possible diagnosis'. The condition was mentioned or discussed by a doctor, the person may have had investigations and some treatment, but this was not consistent with the level of intervention that one would expect from conventional medical practice for a person with this condition.
>
> '4' 'Probable diagnosis'. The condition was diagnosed by a doctor, perhaps with specialist referral, and investigated and treated medically or surgically in a manner consistent with the level of intervention that one would expect from conventional medical practice for a person with this condition.

If the doctor could not determine, after 3 or 4 questions, which category was most appropriate, they were instructed to classify the condition as a 'possible diagnosis'.

5.6.2.3.4 General health questions and additional findings

The doctor asked an open question(s) about the participant's general health and health concerns; and thus provided the opportunity for the participant to raise health concerns and for the doctor to undertake a brief systems review relevant to significant concerns. The doctor re-examined the participant if necessary and recorded any additional findings without altering their previously recorded findings (p39).

5.6.2.3.5 Fitness test

The doctor's assessment included measurement of heart rate in recovery from a standardised step test as an objective and efficient way to classify participants in terms of their aerobic fitness. It is considered that the essentially linear relationship between heart rate and oxygen consumption can be used to estimate a subject's maximum oxygen uptake (VO_2) with a reasonable degree of accuracy.[312] The fitness test complemented the 'Symptoms of tiredness or fatigue' questionnaire as an assessment of fatigability.

The fitness test involved stepping at a designated cadence using a digital metronome, up and back from a 40 centimetre platform for three minutes.[313] Women were required to complete 22 complete step-ups per minute whilst men completed 24 step-ups per minute. Participants were timed using a stopwatch. Participant's pulse rates were measured at 5 seconds and again at 20 seconds after completion of stepping, using a 'Vision Fitness' heart rate monitor. The two measures were then averaged to give a single recovery heart rate in beats per minute for each participant, with lower rates indicating greater aerobic capacity.

Participants undertook the fitness test only if the assessing doctor considered them suitably healthy to complete the test safely and without injury. If the participant was considered not

suitably healthy to complete the test, the reason for this was recorded. Similarly, any known reason was recorded if a participant failed to complete the entire three-minute test.

5.6.2.3.6 Feedback to Participants

All participants were sent a medical report summarising their individual medical assessment and test results. Participants were invited to nominate a medical practitioner to receive a copy of their medical report. If the participant did not wish to nominate a medical practitioner to receive a copy of their medical report, they were not required to do so.

Microsoft Word-based proforma templates were developed to assist the HSA doctors in completing the medical reports. The medical report was divided into sections:

- Medical history,
- Physical examination,
- Blood tests,
- Other special tests - lung function testing, skin prick testing and urine testing,
- Psychological testing.

If any medical conditions were identified which needed urgent follow-up, investigation or treatment the HSA doctor discussed this with the participant at the time of the examination, and provided the person with an 'Urgent' feedback letter for them to take to their medical practitioner. If an abnormality was detected through the examination or testing, it was recommended in the report that the person discusses this with his or her treating doctor.

5.6.3 Telephone questionnaire participants

The telephone questionnaire was offered to subjects who declined to participate in the study's full medical assessment or postal questionnaire, for the purpose of investigating any differences in the demographic profile and general health profile of study participants and non-participants. All questions included in the telephone questionnaire were drawn directly from the postal questionnaire, enabling responses from participants and telephone-only subjects to be directly compared. The information collected included:

- Country of birth
- Level of highest education achieved
- Occupational status
- Smoking history
- Physical Component Summary (PCS-12) and Mental Component Summary (MCS-12) measures from the SF-12 Short Form Health Survey

5.6.4 Consistency and validation measures and other sources of data

5.6.4.1 Access to ship's records

Ships' logs record position, state of readiness, weather and visibility at 8-hour intervals. Chemical and fire alarms, exercises, ships passed, ships boarded, shots fired, mine sighting, injuries and other significant events at sea are also recorded. These were accessed to identify important events such as chemical alarms and significant exposure to SMOIL and dust, both of which would have reduced visibility.

5.6.4.2 Comparison of self-reported information with Defence policies

Self-reported immunisations and use of prophylactic medication such as pyridostigmine bromide were compared with Defence policies.

5.6.4.3 Access to previous medical records

Medical data are kept in the service person's Defence Force medical file. It was not planned to access these data as part of the cross-sectional study, because of likely problems with data quality and completeness, and the large amount of resources required to access, transcribe, enter and manage these data. In addition, it was anticipated that all data required to address the research questions related to the cross-sectional study could be collected during the study. However, consent was sought from participants at the time of the cross-sectional study for this possibility should there later be a need to access these medical records to validate health information.

5.6.5 Blinding

A number of measures were instituted to ensure the nurses, psychologists and doctors undertaking the medical assessments remained blinded, wherever possible, as to whether their participants were a Gulf War veteran or a member of the comparison group. These measures included:

- instruction to the nurses, psychologists and doctors in the training sessions to refrain from discussing the participant's military service histories,
- stapling of the military deployment section of the postal questionnaire by the nurse, so that the doctor remained blinded to these details,
- recording, as part of the data collection by the attending nurse, psychologist or doctor if a participant's Gulf War status was revealed during the medical assessment.

Scheduling of the doctor's physical examination prior to other sections of the doctor's assessment, where medical history and other information was collected from the participant, assisted in blinding the doctors to reported symptoms and medical conditions whilst they undertook the physical examination.

5.6.6 Pilot study

The study recruitment strategy, medical assessment and postal questionnaire were piloted with a sample of 50 subjects (25 Gulf War and 25 comparison group) from Victoria in August 2000. The pilot study gave an indication of the expected response to each stage of recruitment and allowed the Monash University study team to adjust the databases which tracked the progress of the Contact and Recruitment strategy and transferred participants' data to HSA offices. The overall time component allocated to the medical assessment and the structure and content of the medical assessment were refined as a result of the pilot. Some interviewer-administered questionnaires were transferred to the postal questionnaire. The original postal questionnaire items were reviewed and some minor adjustments were made.

The pilot study participant's data was combined with that of the study participants in the analysis.

5.6.7 Study Protocol

After comments on draft versions were sought and incorporated, the final version of the Study Protocol for the Australian Gulf War Veterans' Health Study was distributed to all members of the Scientific Advisory Committee and the Consultative Forum for the study, as well as the Monash University Standing Committee on Ethics in Research Involving Humans, the Department of Veterans' Affairs Human Research Ethics Committee and the Australian Defence Human Research Ethics Committee.

5.6.8 Study Procedures Manuals

The following study Procedure Manuals set out the procedures for the study, and was available in a paper based and electronic form.

Manual I: *Contact and Recruitment Procedures*. This was used by the Department of Veterans' Affairs-based Contact and Recruitment team. It outlined the procedures involved in initiating mail and phone contact with all study cohort members, tracking the outcome of attempts to make contact, appropriate responses to expected queries/questions and the transaction of recruitment information from DVA to HSA and to the Monash University study team.

Manual II: *Administration by Health Services Australia, Head Office*. This was used by HSA administrative and Information Technology staff at HSA Headquarters in Canberra. It covered procedures involved in up-loading new copies of the study database, the weekly receipt and import of new participant data from DVA, re-allocation of participants across HSA offices, and regular export of data to Monash University.

Manual III: *Participant Assessment Procedures.* This was used by HSA administrative and medical assessment teams. This manual covered all appointment making procedures, all medical assessment and other data collection procedures, procedures for completion of medical reports for participants and their nominated medical practitioner, and the transfer of complete data sets to the Monash University study team.

5.6.9 Training

All HSA administration staff, nurses, psychologists and doctors, who were to undertake the administration or medical examination of study participants, were trained in the study procedures. Initially this training was undertaken over three days in Melbourne in September 2000. An introductory session to brief the administrative and medical testing teams included speakers from DVA, Department of Defence, the Monash University study team, the HSA project manager and a senior manager from the Melbourne HSA office where the pilot study was conducted, and a representative of the Consultative Forum. The training was conducted by the Monash University study team, the HSA project manager and experts in certain aspects of the physical testing and data collection such as spirometry, skin prick testing, neurological examination and the administration of the CIDI. Further training sessions were conducted in Melbourne as the need arose throughout the study, including additional spirometry training sessions for the nurses.

Training was conducted on all aspects of HSA staff roles and responsibilities in the study for their role as data collectors and as the public face of the study in their interaction with participants. Standardisation of data collection, quality and completeness of data collection, and ethical aspects of the study including confidentiality were emphasised throughout the training. Special attention was given to ensuring the medical and administrative staff were capable of relating empathically to Gulf War veterans and other military personnel through an understanding of their experiences and traumas.

5.6.10 Communication

During the conduct of the study, the medical testing and administrative teams were in communication with the Monash University study team and HSA management via phone, fax and e-mail to answer questions or address problems. E-mail distribution lists were established to communicate responses or solutions to problems to all appropriate HSA staff in order to ensure consistency and uniformity of data collection in the study. Where monitoring

of data quality revealed problems with an individual or with a testing team, appropriate remedial feedback was given by the Monash University study team or HSA management in consultation with each other as appropriate.

The Monash University study team, HSA, DVA, IMVS and Medvet Science monitored the progress of the study and conducted regular teleconferences and face-to-face meetings. Relevant reports from the tracking database were used to monitor progress and identify any problems to be addressed by the study team.

The Scientific Advisory Committee and Consultative Forum met at regular intervals with the Monash University study team, HSA, DVA and Department of Defence representatives.

5.6.11 Data management

5.6.11.1 Transfer of medical data

When all the blood tests results were available, and the doctor's medical report was completed, a designated person at each HSA office was responsible for collating, checking completeness of, and returning all data for each participant to Monash University. This may have been a registered nurse or administrative officer.

Electronically stored data, such as the spirometry results and data collected in the administration of the CIDI, were saved and transferred directly to Monash University. CIDI data was stored without participants' names attached. An electronic version of the pathology results was also transferred to Monash University on a regular basis. The transfer of this data was password protected to maximise its security.

Paper-based data, such as questionnaire data, was sent by mail directly to Monash University for checking, data entry, storage and analysis.

Where a participant requested that a copy of his/her medical report be sent to a nominated medical practitioner, this would only be done if written and signed consent was received. Participants could use the consent form that was provided for this purpose in the postal questionnaire. Alternatively, Monash University undertook to send separate consent forms to any participant subsequently requesting a copy of their medical report to be sent to a medical practitioner or some other third party. An internal process was established to ensure that signatures on returned consent forms were checked against those on the participant's original study Informed Consent Statement to satisfy the study team that the person requesting the information was actually the participant.

5.6.11.2 Data checking, processing and coding and data entry

A variety of procedures were instituted to ensure completeness of data and accuracy of data entry. These included the following:

- Completed postal questionnaires were checked by the HSA nurses, in the presence of the participant, at the time of the medical examination.
- Completed postal questionnaires and medical examination booklets were checked by Monash staff upon receipt by the research team.
- Where sections of the postal questionnaire were found to be missing or inconsistent in content, the researchers re-contacted study participants by phone, with the aim to retrieve missing data or clarify inconsistent data.
- Where sections of the medical examination data were found to be inconsistent or missing, the researchers provided direct advice and feedback to the medical examination teams.

- All received data was checked against a tracking database to ensure that all separate sources of data for an individual participant (those being the postal questionnaire, medical examination data, spirometry results, CIDI data and pathology tests) were present.
- All postal questionnaire and medical examination booklet data were entered using a double data entry method where each data point was entered twice and cross-matched.
- Upon double-data entry of the first 300 postal questionnaires and medical examination booklets, the researchers checked the data entry accuracy for a ten percent random sample of the questionnaires and booklets, and provided advice and feedback to the data entry company regarding any common areas of error.
- Upon completion of the first two months of data collection, an audit was conducted on the quality of spirometry undertaken by the HSA nurses, with results directly fed back to the HSA medical assessment teams.
- Updated sets of electronic sources of data, those being the spirometry, CIDI and pathology data sets, were requested monthly and checked to ensure that all required records were present and complete.

Several sources of raw data were coded upon receipt by the research team. This included the coding of:
- ADF ranks in to the categories 'Officer', 'Other ranks-supervisory' and 'Other ranks-non supervisory'.
- Individual cancers in to ICD-9 categories based on primary site.
- Individual medications into MIMS categories.

Where responses did not readily fit into a predesignated category, such as various self-reported cancer types or currently used medicines, they were reviewed and assigned a category by a medically qualified member of the study team.

5.6.11.3 Methods to ensure privacy of medical data

Methods to ensure privacy of medical data, that were approved by the Ethics Committees, included initial storage of the paper-based medical and questionnaire data in locked cabinets with a unique study number attached, and equally secure but separate storage of the identifying information. Removal of all identifying information such as participants' names, signatures and address details from the medical data and questionnaires was done after the study data entry and analysis was completed.

Upon completion of data entry, all electronically stored medical and questionnaire data was stored de-identified and with the unique study number attached. Password protection of such electronically stored data ensured that only those staff responsible for its processing and analysis were allowed access. Similarly, only those staff responsible for data processing handled the paper-based data. All such staff were required to sign confidentiality agreements protecting the security of any data they processed.

5.6.11.4 Long-term storage of data

Monash University will keep copies of the information for the seven year period required under the NHMRC guidelines for epidemiological research.

All de-identified data will be transferred to the Department of Veterans' Affairs at the end of the project for long-term storage, Data analysis and statistics

5.6.11.5 Data quality

Methods used to ensure optimal data quality are described throughout this report and included:

- the use of standardised data collection instruments and procedures,
- the use of previously validated data collection instruments and procedures wherever possible,
- training of interviewers,
- standardisation and calibration of equipment,
- blinding of interviewers as to Gulf War status,
- double entry and independent random checking of paper based data, and
- rigorously controlled data checking, coding and cleaning procedures.

5.6.11.6 Confounders and bias

Confounders may be defined as variables that are not of primary interest but which may have an effect on the outcome variables.[314] Information was collected on potential confounders such as cigarette smoking and alcohol intake. The effects of such confounders were controlled, or adjusted for, in the statistical analyses.

Potential sources of bias that may affect the validity of the results included participation or selection bias, information bias, observer bias and recall bias.[314, 315] Participation bias, which may result from eligible participants not participating in the study and being different in some way from those who did participate, was minimised by taking all necessary steps to contact eligible people and encouraging them to participate (sections 5.5.2 and 5.5.3).

Information bias due to measurement error was also a potential problem, especially with the use of psychological symptoms and other data obtained by questionnaire. Some duplication of health outcome measures, in the postal questionnaire and the interviewer-administered health assessment instruments, were used to test for consistency. We also employed questionnaires that had been validated in other similar populations. To minimise observer bias the researchers instituted procedures that ensured that the data collectors were blinded to the respondent's Gulf War status wherever possible. The comprehensive training of data collectors should also have minimised inter-observer variability. Recall bias was also an anticipated problem, as it had been more than ten years since the time of the Gulf War, and Gulf War veterans may have been more likely to recall exposures than the comparison group.[35, 316] Those veterans experiencing a higher number of symptoms, or other adverse health outcomes, may also have been more likely to recall exposures.

5.6.11.7 Power considerations

With approximately 1500 Gulf War veterans and 1500 comparison group subjects providing information on symptoms, this study was determined to have at least 90% power, at a two-sided 5% significance level, to detect increases in the prevalence of symptoms, or defined cases, in Gulf War veterans of the order of 20% to 100% (corresponding to odds ratios of 1.3 to 2.0) for symptoms with a prevalence of 2% to 30% (in reverse order) among the comparison group.

For psychological conditions, the expected prevalences for many of the conditions were based on the results of the Australian National Survey of Mental Health and Wellbeing of Adults, and these were likely to be in the range of 10-20%.[260] Based on these expected

prevalences, the study was determined to have sufficient power to detect clinically meaningful differences.

For categorical outcome variables with a very low prevalence, ie less than 2%, the study would only be able to detect large increases in risk and the point estimates are likely to have large confidence intervals. It is only for the higher prevalence outcomes that subgroup analyses were considered to be feasible.

For exposure-response relationships, an estimate of the size of detectable effects can be gained by categorising exposure (eg combat or environmental) among Gulf War veterans into four equally sized intervals, or quartiles. With 1500 Gulf War veterans the detectable odds ratio (defined below), of symptom prevalence per unit increase in exposure category with 90% power, ranged from 1.2 (for a symptom with prevalence among Gulf War veterans of 30%) to 1.8 (for a symptom with prevalence of 2%). Broader categorisation of exposure (eg presence or absence on ships exposed to smoke from oil fires), and assuming 50% of Gulf War veterans exposed, yield detectable prevalence ratios ranging from 1.3 to 2.6 for non-exposed symptom prevalence of 30% to 2% respectively.

For outcomes measured on a continuous scale (eg FEV_1 and other lung function measurements) the study had power to detect very small effects. For example, assuming a mean FEV_1 in the comparison group of 3.5 litres with an SD of 0.5, 1500 veterans per group will allow detection of a reduction of 2% in mean FEV_1 among Gulf War veterans with at least 95% power at a 5% significance level. In general, the sample size afforded 95% power to detect a difference between Gulf War veterans and comparison group in the order of 0.12 standard deviations.

5.6.11.8 Statistical analysis

The statistical analyses involved a cross-sectional comparison of the Gulf War veterans and comparison group with respect to symptoms measured on dichotomous (eg 'never', 'yes') or Likert-type scales,[265] (eg 'better than usual', 'same as usual', 'less than usual') and other measurements made on continuous scales.

Differences in the prevalence of symptoms in Gulf War veterans were quantified using odds ratios. The odds of a particular symptom may be defined as the number of persons who have the particular symptom present divided by the number of persons who do not have that particular symptom present.[317] An odds ratio is therefore defined in this study as the odds of having a symptom present in one group (in this case the Gulf War veterans) divided by the odds of having that symptom present in another group (in this case the comparison group). An odds ratio may range in value from zero to infinity. In terms of the present study, an odds ratio that is larger than one occurs when the odds of having a particular symptom present is higher in the Gulf War Veterans than in the comparison group; and in this situation the prevalence of the condition is also greater in the Gulf War Veterans than in the comparison group. An odds ratio that is less than one has the reverse interpretation. An odds ratio equalling one would indicate that the Gulf War and comparison groups had equal odds and prevalence of a symptom. Odds ratios and their confidence intervals[318] and significance tests were first calculated using the symptoms data only (crude odds ratios), and then modelled by logistic regression,[319] which estimated the odds ratio after accounting for factors involved in the sample selection process and potential confounding factors such as level of education (adjusted odds ratios). If the cell sizes for Gulf War or comparison groups were small (arbitrarily but conventionally defined as being five or less), exact logistic regression was performed.[320]

Outcomes involving counts (eg total number of self-reported symptoms) were analysed using negative binomial regression.[321] Continuous outcomes, and sums of dichotomous or Likert scaled items (eg total score on the Posttraumatic Stress Disorder Checklist) were initially compared between groups using descriptive statistics, and t-tests or nonparametric equivalents (Mann-Whitney / Wilcoxon rank sum tests[322]) and then, after adjusting for matching and confounding factors, using multiple linear regression.[323] If distributional assumptions were not satisfied, median regression,[324] which models the median of the distribution of the outcome rather than the mean (or equivalently minimises the sum of the absolute value of the residuals), was performed. Confidence intervals and significance tests for median regression parameters were computed using 1000 bootstrap[325] replications. In other cases of regression modelling where the requisite normal distribution assumption was met apart from a number of outliers, robust regression,[326] which iteratively downweights outlying observations until stable weights are reached, was performed.

Initial analyses focused on broad comparisons of Gulf War veterans and the comparison group adjusting for age (in four categories: <20, 20-24, 25-35,>35), rank, service type, education and marital status. Interactions (effect modification) of deployment group with age, rank and service type were performed for all outcomes, and were assessed using Wald or likelihood ratio tests.[319]

More detailed comparisons of subgroups of Gulf War veterans, utilising measures such as rank and service type, combat, environmental and chemical exposures were performed; and, in particular, assessment of the existence and magnitude of an exposure-response trend in symptom prevalence across exposure categories. Where a more exact measure of exposure was available, exposure-response trends were computed using the exposure as a linear variable in the regressions. The exposure-response comparisons, being made within the Gulf War group, were thought to be free of any "healthy soldier" effect, which may otherwise exist in comparisons with the non-deployed personnel. Unless indicated otherwise, statistical analyses were predominantly performed using Stata,[327] and data transformation was predominantly performed using SPSS[328] software packages.

Throughout this report we employed a model-based mode of statistical inference,[329] in which the interest centres on describing the (unknown) relationship between measures of current health status and deployment to the Gulf War, service type, age, rank, other background characteristics and relevant exposures. These relationships are expressed by probability models, with the particular health outcomes of individuals randomly sampled for inclusion in this study assumed to be a stochastic (ie, random) realisation from these probability models. As all factors involved in the stratified sampling scheme (ie, service type, age, rank and gender) are incorporated into the probability models, unweighted methods of estimation are used throughout.

Some authors choose an alternative mode of statistical inference in which health outcomes of all individuals are regarded as deterministic rather than stochastic. The only source of uncertainty in observed relationships between current health status and deployment and other factors is regarded as arising from the taking of a random sample as opposed to a complete census of the entire military population eligible for deployment at the time of the Gulf War. In this sense the population of persons eligible for Gulf War deployment represents a fixed and finite population. A series of statistical analyses using this "finite population" approach was conducted for the analysis of self-reported health symptoms, medical conditions and psychological diagnoses. These analyses incorporated sampling weights, stratification and finite population correction factors. The resulting odds ratios were generally within 5% to

10% of the unweighted odds ratios presented in this report, with 95% confidence intervals generally 5% to 10% narrower than their unweighted counterparts. The rather small gains in precision arise due to the expected gain in precision from the use of finite population correction factors being offset by the inefficiency of a large variation in sampling weights, particularly for the Army and Air Force comparison group sampled subjects.

5.6.11.9 Exploration of symptom clusters

In order to investigate whether there was a unique pattern of self-reported symptoms present in the Gulf War veterans that was not also present in the comparison group, exploratory factor analyses[330] were performed using the Mplus structural equation modelling program.[203] [331] Details of these procedures are given in Chapter 18.

5.6.12 Research Team

Because of the multidisciplinary nature of this study, a research team with a wide range of medical and research skills was established.

The investigators based in the Department of Epidemiology & Preventive Medicine at Monash University were:

- Assoc Prof Malcolm Sim, occupational physician and Principal Investigator
- Assoc Prof Michael Abramson, respiratory physician and epidemiologist
- Assoc Prof Andrew Forbes, biostatistician
- Dr Karin Leder, infectious diseases physician
- Prof John McNeil, physician and epidemiologist.

The investigators based in other institutions were:

- Dr Lin Fritschi, cancer epidemiologist, University of Western Australia (an investigator for the cancer and mortality study), and
- Dr Harry Schwarz, medical practitioner and Project Manager for HSA.

Advice was sought from Assoc Prof Mark Creamer of the Australian Centre for Posttraumatic Mental Health, Heidelberg, on the design and interpretation of the psychometric tests and the military service experiences questionnaire.

Assoc Prof Andrew Mackinnon, psychologist and biostatistician, of the School of Psychology, Psychiatry and Psychological Medicine, Monash University, and the Biostatistics and Psychometrics Unit, Mental Health Research Institute, Parkville, was consulted regarding factor analytic and structural equation modelling methods.

Assoc Prof Richard Macdonell, neurologist and Deputy Director of Neurology, Austin & Repatriation Medical Centre, Heidelberg, was consulted regarding analysis and interpretation of neurological health outcomes.

During the course of the study, Assoc Prof Christopher Fairley accepted a position as Professor Director, University of Melbourne Sexual Health Centre, and due to the demands of his new position he indicated with regret that he would be unable to continue as an investigator on this study. Dr Karin Leder, an infectious diseases physician appointed to the Department of Epidemiology & Preventive Medicine, was invited to join the study team.

Other members of the Monash University study team included:

- Dr Helen Kelsall, public health physician and senior research fellow,
- Ms Jill Ikin, data manager and study coordinator,
- Dr Deborah Glass, occupational hygienist,

- Mr Dean McKenzie, biostatistician,
- Mr Peter Ittak, research assistant
- Mr Ewan MacFarlane, research assistant and
- Ms Koraly Giuliano, computer programmer.

Ms Emma Conyers, Ms Julie Attard, Ms Jane Ball and Ms Lucia MacFarlane provided administrative support.

5.6.12.1 The Department of Epidemiology & Preventive Medicine, Monash University

The Department of Epidemiology & Preventive Medicine is a major department of the Faculty of Medicine, Nursing and Health Sciences of Monash University. It comprises several research units and plays a leading role in research in many areas of clinical research and public health in Australia. It has a strong track record in gaining nationally competitive research grants, including those from the NHMRC. The department has strong clinical links with the Alfred Hospital and has several long-term epidemiological studies in progress. The Department's Unit of Occupational and Environmental Health has extensive experience of such health studies in working populations, with a particular interest in exposure assessment.

5.6.12.2 Health Services Australia

The study was undertaken in collaboration with Health Services Australia Limited (HSA). HSA is a national organisation, specialising in occupational health, health assessment and psychology services. The core ethos of HSA is to provide independent and objective professional advice. HSA is the first provider of corporate, medical and health services to achieve ISO 9002 Quality Certification in Australia. HSA offices are fully equipped and able to perform complete health assessments, psychological testing and physical and functional capacity evaluations.

The HSA offices are located in every capital city and a number of provincial centres around Australia as detailed in section 5.5.6

Dr Harry Schwarz, a medical practitioner with extensive management experience, coordinated and managed HSA's responsibilities in the study. His predecessor, Dr Michael Pincus, unfortunately passed away during the course of the study. Dr Pincus' role in the early development and conduct of the study is gratefully acknowledged.

5.6.13 Scientific Advisory Committee

A Scientific Advisory Committee, appointed by DVA, provided advice on the development, conduct and analysis of the study. The SAC met regularly with study investigators and Department of Veterans' Affairs and Department of Defence representatives. The members of this Committee were:

- Prof Terry Dwyer AM (Chair), epidemiologist
- Dr Leigh Blizzard, biostatistician
- Dr Kerry Delaney, anaesthetist and occupational physician with expertise in chemical, biological and nuclear defence; Commanding Officer of the First Task Group Medical Support Element during the Gulf War
- Prof Alexander McFarlane, psychiatrist, and
- Prof Tania Sorrell, infectious diseases physician.

5.6.14 Consultative Forum

A Consultative Forum represented and consulted with the veteran community, and in turn fed back information to its constituent members. The members of the Consultative Forum represented:

- Aboriginal and Torres Strait Islander Veterans and Services Association (ATSIVSA),
- Armed Forces Federation of Australia (AFFA),
- The Australian Defence Force,
- Australian Federation of Totally and Permanently Incapacitated Ex-Servicemen and Women (TPI),
- Australian Gulf War veterans Association (AGWVA),
- Australian Veterans and Defence Services Council (AVADSC),
- The Department of Veterans' Affairs,
- Gulf War veterans' Health Study Scientific Advisory Committee,
- Health Services Australia (HSA),
- Incapacitated Servicemen and Women's Association of Australia (ISWAA),
- Monash Gulf War Veterans' Health Study Team,
- National Consultative Group of Service Families,
- Naval Association of Australia,
- Office of the Minister for Veterans' Affairs,
- Regular Defence Force Welfare Association (RDFWA), and
- Returned and Services League of Australia Ltd (RSL).

5.6.15 Ethics Committees' Approvals

The study was approved by the following Ethics Committees:

- The Monash University Standing Committee on Ethics in Research Involving Humans,
- The Department of Veterans' Affairs Human Research Ethics Committee,
- The Australian Defence Human Research Ethics Committee.

Letters of endorsement from each of these Committees are provided in appendix 7.

6. Recruitment

This chapter describes the results of the recruitment effort for this study, including a comparison of participants and non-participants. Recruitment for this study commenced in July 2000 with weekly mail-outs of invitation packages to Navy subjects. These were followed by mail-outs to Air Force subjects commencing in February 2001 and mail-outs to Army subjects commencing in May 2001. Sampling for each service type was conducted within the 8 weeks prior to each wave of mail-outs. Recruitment was closed in April 2002. A complete guide to the subject sampling methods, study inclusion and exclusion criteria, sample sizes and contact and recruitment methods, including methods to maximise recruitment success and minimise participation bias, can be found at chapter 5.

6.1 Recruitment categories

The original study sample comprised 1873 Gulf War veterans and 3192 comparison group subjects. Throughout the contact and recruitment period, they were classified into the following categories.

6.1.1 Ineligible subjects

It was assumed, upon commencement of the contact and recruitment effort, that some sampled subjects would prove to be ineligible for participation according to the study inclusion criteria. The original comparison group was specifically over-sampled on the assumption that some Navy subjects would prove to have been not serving at the time of the Gulf War and therefore ineligible for inclusion in the study. It was not known whether any of the Gulf War veteran group, identified from the Nominal Roll, would prove to be ineligible for participation. Ineligible subjects were usually identified by information that they provided to the contact and recruitment team.

6.1.2 Eligible subjects

Throughout the contact and recruitment period, and upon cessation of the contact and recruitment effort, remaining eligible subjects were classified as belonging to one of the following recruitment categories:

6.1.2.1 Not recruitable categories

Eligible subjects were classified as not recruitable if they were:

- *Reportedly deceased*: These persons had either already been identified as deceased according to DVA records, or were reported as being deceased during the study contact and recruitment period.
- *Reportedly overseas long-term*: These persons were found to be overseas during the study contact and recruitment period with no expectation of returning to Australia during the data collection period.

6.1.2.2 Recruitable categories

Remaining eligible subjects were considered recruitable. These subjects were classified into the following categories:

Participants

- *Full participant*: These persons completed the study postal questionnaire and attended a medical assessment with HSA.
- *Postal questionnaire-only participant*: These persons completed the study postal questionnaire but did not attend a medical assessment with HSA.

Non-participants

- *Telephone questionnaire-only*: These persons completed the telephone-administered heath questionnaire only, and declined all other participation.
- *Declined all participation*: These persons declined participation in all aspects of data collection including the medical assessment, postal questionnaire and telephone questionnaire.
- *Not Contactable*: It was assumed that the study invitation packages were not received by these subjects. There was evidence to suggest that the held contact details were incorrect, and no alternative contact details could be found.
- *Non-responder*: In these cases there was evidence that the Contact and Recruitment team had the correct contact details and that the subject had received the invitation package. Despite multiple contacts, or multiple contact attempts, these subjects never finally indicated whether they wished to participate or refuse.

6.2 Recruitment results

6.2.1 Final eligible sample sizes

Of the original 1873 Gulf War veterans, one proved to have been a serving member of the British armed forces during the Gulf War, and not the ADF, and two reported to have not deployed to the Gulf War. All three subjects were therefore categorised as ineligible for participation in the Gulf War veteran group and were removed from the eligible sample. One comparison group subject reported to have deployed to the Gulf War. This report was confirmed by the ADF and this comparison group subject was reclassified as a Gulf War veteran for the purpose of the study. The final Gulf War veteran sample totalled 1871 veterans, which included 38 females.

Throughout the recruitment period 267 comparison group subjects, of the originally sampled 3192, were found to be ineligible for inclusion in the study as they had not been serving members of the ADF in August 1990. These subjects were therefore removed from the comparison group sample along with the one subject who reported deploying to the Gulf War. The resulting eligible comparison group sample totalled 2924 including 74 females.

6.2.2 Recruitment outcomes for Gulf War veterans and the comparison group

6.2.2.1 Total eligible sample

The recruitment results for the total eligible sample, and for the total recruitable sample, are shown in Table 6.1 for Gulf War and comparison group subjects. Table 6.1 also shows the recruitment results for both study groups according to their ADF employment status; that is, whether they were classified as still serving members of the ADF, or not serving, at the time of sampling. Sampling dates were approximately June 2000 for the Navy subjects, January 2001 for the Air Force and April 2001 for the Army.

Of 1871 Gulf War veterans, removal of subjects who were reportedly deceased and reportedly overseas long-term resulted in a total recruitable sample of 1808 Gulf War veterans. Among these there was an overall participation rate of 80.5% (1456/1808), with 1414 Gulf War veterans (78.2%) completing both the medical assessment and postal questionnaire, and a further 42 (2.3%) completing the postal questionnaire alone. These included 32 female Gulf War veteran participants, 30 of whom completed both the medical assessment and the postal questionnaire.

The total recruitable sample of comparison group subjects was 2796 after removal of those reportedly deceased and reportedly overseas long-term. The overall participation rate in the comparison group was 56.8% (1588/2796) with 1588 participants of whom 40 were females. Compared with the Gulf War veteran group participants, the comparison group participants were less likely to participate in full (50.5% of the recruitable sample) and more likely to opt for postal questionnaire-only participation (6.3%). Overall the comparison group subjects were also more likely than the Gulf War veterans to participate in the telephone questionnaire, more likely to decline all participation and more likely to be classified as non-responders or not contactable.

Within both study groups, subjects classified as serving members of the ADF at the time of sampling were more likely to participate in full, or else were more likely to participate as postal questionnaire-only participants when compared with those no longer serving. Serving members were also less likely to be not contactable compared with not serving subjects.

Telephone questionnaire data was collected on a total of 411 subjects, representing more than 21% of all Gulf War veteran non-participants (77/352) and more than 27% of all comparison group non-participants (334/1208).

It should be noted that the tabulation of three Gulf War veterans, and 17 comparison group subjects, who were 'reportedly deceased' and yet also categorised as still serving with the ADF at the time of sampling, is likely to be the result of some misclassification of serving status, rather than the incidence of 20 new deaths in the period between sampling and recruitment closure.

6.2.2.2 Eligible sample by service type

The recruitment results for eligible Navy subjects, Army subjects and Air Force subjects are shown in Table 6.2, Table 6.3 and Table 6.4 respectively, for Gulf War veterans and comparison group subjects, and for those considered serving or not serving at the time of sampling.

Overall, Navy subjects represented 86% of all Gulf War veteran participants (1249/1456) and 72% of all comparison group participants (1139/1588). The participation rates within the service types were highest for the Navy Gulf War veteran group with 81.6% of this group participating either in full or via postal questionnaire alone (1249/1530), compared with 78.5% of Army Gulf War veterans (95/121), and 71.3% of Air Force Gulf War veterans (112/157). Participation rates, in the comparison group, were fairly consistent across the three service types and lower than those for Gulf War veterans.

Among Gulf War veterans, those who served in the Air Force were the least likely to participate in full and the most likely to decline all participation in the study, when compared with Gulf War veterans of the Navy and Army services.

Table 6.1 Recruitment results for all Gulf War veterans and comparison group subjects.

	All Gulf War veterans						All comparison group							
	Serving		Not serving		Total GWV		Serving		Not serving		Total comp grp		Study Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total eligible sample	743	(39.7)	1128	(60.3)	1871		1099	(37.6)	1825	(62.4)	2924		4795	
Reportedly deceased	3	(0.4)	19	(1.7)	22	(1.2)	17	(1.5)	14	(0.8)	31	(1.1)	53	(1.1)
Reportedly overseas long-term	14	(1.9)	27	(2.4)	41	(2.2)	41	(3.7)	56	(3.1)	97	(3.3)	138	(2.9)
	Serving		**Not serving**		**Total GWV**		**Serving**		**Not serving**		**Total comp grp**		**Study Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total recruitable sample	726		1082		1808		1041		1755		2796		4604	
Participants														
Full participant	589	(81.1)	825	(76.2)	1414	(78.2)	555	(53.3)	856	(48.8)	1411	(50.5)	2825	(61.4)
Postal quest only	24	(3.3)	18	(1.7)	42	(2.3)	80	(7.7)	97	(5.5)	177	(6.3)	219	(4.8)
Non-participants														
Telephone quest only	32	(4.4)	45	(4.2)	77	(4.3)	153	(14.7)	181	(10.3)	334	(11.9)	411	(8.9)
Declined all participation	38	(5.2)	82	(7.6)	120	(6.6)	188	(18.1)	309	(17.6)	497	(17.8)	617	(13.4)
Non-responders	41	(5.6)	27	(2.5)	68	(3.8)	51	(4.9)	76	(4.3)	127	(4.5)	195	(4.2)
Non-contactables	2	(0.3)	85	(7.9)	87	(4.8)	14	(1.3)	236	(13.4)	250	(8.9)	337	(7.3)

Table 6.2 NAVY: Recruitment results for Navy Gulf War veterans and comparison group subjects

	Navy Gulf War veterans						Navy comparison group							
	Serving		Not serving		Total GWV		Serving		Not serving		Total comp grp		Study Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total eligible sample	603	(38.2)	976	(61.8)	1579		712	(33.6)	1405	(66.4)	2117		3696	
Reportedly deceased	2	(0.3)	15	(1.5)	17	(1.1)	10	(1.4)	11	(0.8)	21	(1.0)	38	(1.0)
Reportedly overseas long-term	12	(2.0)	20	(2.0)	32	(2.0)	31	(4.4)	34	(2.4)	65	(3.1)	97	(2.6)
	Serving		**Not serving**		**Total GWV**		**Serving**		**Not serving**		**Total comp grp**		**Study Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total recruitable sample	589		941		1530		671		1360		2031		3561	
Participants														
Full participant	488	(82.9)	733	(77.9)	1221	(79.8)	366	(54.5)	667	(49.0)	1033	(50.9)	2254	(63.3)
Postal quest only	13	(2.2)	15	(1.6)	28	(1.8)	45	(6.7)	61	(4.5)	106	(5.2)	134	(3.8)
Non-participants														
Telephone quest only	20	(3.4)	41	(4.4)	61	(4.0)	106	(15.8)	145	(10.7)	251	(12.4)	312	(8.8)
Declined all participation	32	(5.4)	64	(6.8)	96	(6.3)	120	(17.9)	241	(17.7)	361	(17.8)	457	(12.8)
Non-responders	36	(6.1)	17	(1.8)	53	(3.5)	27	(4.0)	48	(3.5)	75	(3.7)	128	(3.6)
Non-contactables	0	(0.0)	71	(7.5)	71	(4.6)	7	(1.0)	198	(14.6)	205	(10.1)	276	(7.8)

Table 6.3 ARMY: Recruitment results for Army Gulf War veterans and comparison group subjects

	Army Gulf War veterans						Army comparison group							
	Serving		Not serving		Total GWV		Serving		Not serving		Total comp grp		Study Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total eligible sample	70	(56.9)	53	(43.1)	123		182	(54.0)	155	(46.0)	337		460	
Reportedly deceased	1	(1.4)	0	(0.0)	1	(0.8)	2	(1.1)	0	(0.0)	2	(0.6)	3	(0.7)
Reportedly overseas long-term	1	(1.4)	0	(0.0)	1	(0.8)	2	(1.1)	4	(2.6)	6	(1.8)	7	(1.5)
	Serving		**Not serving**		**Total GWV**		**Serving**		**Not serving**		**Total comp grp**		**Study Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total recruitable sample	68		53		121		178		151		329		450	
Participants														
Full participant	55	(80.9)	38	(71.7)	93	(76.9)	87	(48.9)	71	(47.0)	158	(48.0)	251	(55.8)
Postal quest only	2	(2.9)	0	(0.0)	2	(1.7)	11	(6.2)	11	(7.3)	22	(6.7)	24	(5.3)
Non-participants														
Telephone quest only	3	(4.4)	0	(0.0)	3	(2.5)	15	(8.4)	11	(7.3)	26	(7.9)	29	(6.4)
Declined all participation	2	(2.9)	5	(9.4)	7	(5.8)	41	(23.0)	26	(17.2)	67	(20.4)	74	(16.4)
Non-responders	4	(5.9)	3	(5.7)	7	(5.8)	18	(10.1)	16	(10.6)	34	(10.3)	41	(9.1)
Non-contactables	2	(2.9)	7	(13.2)	9	(7.4)	6	(3.4)	16	(10.6)	22	(6.7)	31	(6.9)

Table 6.4 AIR FORCE: Recruitment results for Air Force Gulf War veterans and comparison group subjects

	Air Force Gulf War veterans						Air Force comparison group							
	Serving		Not serving		Total GWV		Serving		Not serving		Total comp grp		Study Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total eligible sample	70	(41.4)	99	(58.6)	169		205	(43.6)	265	(56.4)	470		639	
Reportedly deceased	0	(0.0)	4	(4.0)	4	(2.4)	5	(2.4)	3	(1.1)	8	(1.7)	12	(1.9)
Reportedly overseas long-term	1	(1.4)	7	(7.1)	8	(4.7)	8	(3.9)	18	(6.8)	26	(5.5)	34	(5.3)
	Serving		**Not serving**		**Total GWV**		**Serving**		**Not serving**		**Total comp grp**		**Study Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total recruitable sample	69		88		157		192		244		436		593	
Participants														
Full participant	46	(66.7)	54	(61.4)	100	(63.7)	102	(53.1)	118	(48.4)	220	(50.5)	320	(54.0)
Postal quest only	9	(13.0)	3	(3.4)	12	(7.6)	24	(12.5)	25	(10.2)	49	(11.2)	61	(10.3)
Non-participants														
Telephone quest only	9	(13.0)	4	(4.5)	13	(8.3)	32	(16.7)	25	(10.2)	57	(13.1)	70	(11.8)
Declined all participation	4	(5.8)	13	(14.8)	17	(10.8)	27	(14.1)	42	(17.2)	69	(15.8)	86	(14.5)
Non-responders	1	(1.4)	7	(8.0)	8	(5.1)	6	(3.1)	12	(4.9)	18	(4.1)	26	(4.4)
Non-contactables	0	(0.0)	7	(8.0)	7	(4.5)	1	(0.5)	22	(9.0)	23	(5.3)	30	(5.1)

6.3 Comparison of study participants and non-participants.

A comparison of known information for study participants and non-participants was conducted to assess the level to which participants were representative of the recruitable samples from which they were drawn. For these investigations the group referred to as 'participants' include all subjects belonging to the two recruitable categories 'Full participants' and 'Postal questionnaire-only participants' as defined in section 6.1.2.2.

The investigation of differences between participants and non-participants was conducted in two ways. Firstly, all participants were compared with all non-participants, in other words those remaining recruitable subjects who either, only completed the telephone questionnaire, declined all participation, were non-responders, or were not-contactable. Secondly, all participants were compared with the 'telephone questionnaire-only' subjects.

6.3.1 Participants compared with all non-participants.

The information available for all sampled subjects, and therefore available for the comparison of participants with all non-participants, were:

- Age at August 1990 (commencement of the Gulf War),
- Sex
- Service type (Navy, Army or Air Force) at 2 August 1990
- Service rank at August 1990
- ADF employment status (serving versus not serving) at the time of sampling.

The mean age and participation rates within subcategories of each variable are shown in Table 6.5 for Gulf War veterans and the comparison group.

Generally, the characteristics of participants across both study groups were similar. Subjects who were the youngest and the lowest in rank were least likely to participate in both groups. This difference, across age and rank subcategories, was more pronounced in the comparison group where subjects aged less than 20 years, at August 1990, were 30% less likely to participate in the study compared with subjects aged 35 years or older, and non-supervisory ranks were 21% less likely to participate than officer ranks. The source of rank category, at August 1990 for the comparison of participants and non-participants, was DVA-held archival records. Some inaccuracies are thought to have existed within that data source. These inaccuracies are expected to have occurred in both study groups and are not expected to have notably altered the true trend in participation rates across rank category.

As previously noted, Air Force Gulf War veterans were less likely to participate than Gulf War veterans of the Navy and Army. In the comparison group, however, participation was highest in the Air Force group.

Serving subjects were more likely to participate than non-serving subjects, in both groups.

Table 6.5 Mean age and participation rates across age category, sex, service type, rank and ADF employment status in recruitable Gulf War veterans and comparison group subjects: study participants versus all non-participants.

	Gulf War veterans				Comparison group			
		Participants (N=1456)	Non-participants (N=352)			Participants (N=1588)	Non- participants (N=1208)	
Age in years at	**Total**	**Mean (SD)**	**Mean (SD)**		**Total**	**Mean (SD)**	**Mean (SD)**	
2 Aug 1990	1808	27.4 (6.4)	26.1 (6.2)		2796	28.3 (6.4)	26.3 (6.2)	
Age category	**Total**	**n**	**n**	**Participation rate (%)**	**Total**	**n**	**n**	**Participation rate (%)**
<20	234	177	57	(75.6)	324	129	195	(39.8)
20-24	543	420	123	(77.3)	807	414	393	(51.3)
25-34	824	682	142	(82.8)	1311	797	514	(60.8)
≥35	207	177	30	(85.5)	354	248	106	(70.1)
Sex								
Male	1770	1424	346	(80.5)	2723	1548	1175	(56.8)
Female	38	32	6	(84.2)	73	40	33	(54.8)
Service type								
Navy	1530	1249	281	(81.6)	2031	1139	892	(56.1)
Army	121	95	26	(78.5)	329	180	149	(54.7)
Air Force	157	112	45	(71.3)	436	269	167	(61.7)
Rank								
Officer	404	323	81	(80.0)	692	425	267	(61.4)
Other rank-supervisory	1149	951	198	(82.8)	1654	981	673	(59.3)
Other rank-non supervisory	255	182	73	(71.4)	450	182	268	(40.4)

	Gulf War veterans				Comparison group			
		Participants (N=1456)	Non-participants (N=352)			Participants (N=1588)	Non- participants (N=1208)	
Age in years at	**Total**	**Mean (SD)**	**Mean (SD)**		**Total**	**Mean (SD)**	**Mean (SD)**	
2 Aug 1990	1808	27.4 (6.4)	26.1 (6.2)		2796	28.3 (6.4)	26.3 (6.2)	
ADF status	**Total**	**n**	**n**	**Participation rate (%)**	**Total**	**n**	**n**	**Participation rate (%)**
Serving	726	613	113	(84.4)	1041	635	406	(61.0)
Not serving	1082	843	239	(77.9)	1755	953	802	(54.3)

6.3.2 Comparison of study participants with telephone questionnaire-only subjects

The telephone questionnaire was specifically offered to subjects who declined to participate in the study's full medical assessment or postal questionnaire, for the purpose of investigating any differences in the demographic profile and general health profile of study participants and non-participants. All questions included in the telephone questionnaire were drawn directly from the postal questionnaire, enabling responses from participants and telephone-only subjects to be directly compared. The information collected included:

- Country of birth
- Level of highest education achieved
- Occupational status
- Smoking history
- Physical Component Summary (PCS) and Mental Component Summary (MCS) measures from the SF-12 Short Form Health Survey.

The comparison of study participants and telephone questionnaire-only participants is shown in Table 6.6. There were only minor differences in country of birth, occupational status and smoking history. Fewer of the telephone questionnaire-only participants had post-secondary education, possibly because officers were more likely to participate in the study (see Table 6.5) and officer training includes the attainment of a tertiary degree. Telephone questionnaire-only subjects received higher MCS scores (self-reported evidence of healthier mental status) than full participants in both the Gulf War veteran group and the comparison group. PCS scores were also a little higher (self-reported evidence of greater physical functioning) for telephone questionnaire-only subjects.

Telephone questionnaire-only subjects comprised only one quarter of all non-participants. Before any true interpretation can be made of differences between study participants and non-participants it is important to consider how representative the telephone questionnaire-only subjects are of the larger non-participant group. Therefore a comparison was made between telephone questionnaire-only subjects and the remainder of the non-participants on age, service type, service rank and ADF employment status (data not shown).

In the comparison group, where non-participation was highest, it was found that the mean age for telephone questionnaire-only subjects was 26.5 years; very similar to the mean age of 26.2 years for remaining comparison group non-participants. When analysed by age category, the telephone questionnaire-only subjects were slightly under-represented in the <20-year age group (12.9% versus 17.4%). Therefore, comparison group non-participants who did not complete the telephone questionnaire were a little younger than the non-participants who did complete the telephone questionnaire. The comparison group telephone questionnaire-only subjects were more likely to be serving than the other non-participants (45.8% versus 28.9%). Comparison group telephone questionnaire-only subjects were also more likely to have served with a non-supervisory rank (26.3% versus 11.4%).

Patterns between Gulf War veteran telephone questionnaire-only subjects and other non-participants were similar to those in the comparison group.

Table 6.6 Comparison of study participants with telephone questionnaire-only subjects.

	Gulf War veterans				Comparison group			
	Participants (N=1456)		Telephone questionnaire (N=77)		Participants (N=1588)		Telephone questionnaire (N=334)	
	n	(%)	N	(%)	n	(%)	n	(%)
Country of birth								
Australia	1221	(83.9)	63	(81.8)	1324	(83.4)	280	(83.8)
Other	231	(15.9)	14	(18.2)	263	(16.6)	54	(16.2)
Education level								
Up to year 12	542	(37.2)	38	(49.4)	518	(32.6)	166	(49.7)
Certif/Dipl/Tertiary	910	(62.5)	39	(50.6)	1066	(67.1)	168	(50.3)
Occupational status								
Paid employment	1335	(91.7)	70	(90.9)	1468	(92.4)	307	(91.9)
Other	119	(8.2)	5	(6.5)	116	(7.3)	24	(7.2)
Smoking status								
Current	375	(25.8)	18	(23.4)	366	(23.0)	93	(27.8)
Former	444	(30.5)	21	(27.3)	508	(32.0)	102	(30.5)
Never	634	(43.5)	38	(49.4)	710	(44.7)	138	(41.3)
	Median (range)		**Median (range)**		**Median (range)**		**Median (range)**	
SF-12								
Physical Component Summary	52.2 (12.6 – 65.1)		53.8 (22.5 – 59.4)		53.1 (15.6 – 66.8)		54.2 (18.4 – 65.5)	
Mental Component Summary	50.9 (10.1 – 66.1)		56.8 (24.0 – 67.3)		54.0 (16.9 – 69.5)		55.9 (15.9 – 65.7)	

6.4 Investigation of possible participation bias

Having discovered that participation in the study was lower in the comparison group than in the Gulf War veteran group, and lower also among younger persons and lower ranks, we investigated whether this non-response might bias the results of various health outcomes. Bias might arise if the health status of non-participants differed markedly, on average, from the health status of participants. In particular, we investigated the likely direction and possible magnitude of any such bias.

A complete examination of possible participation bias would require the collection of comprehensive information on the health status of all non-participating Gulf War veteran and comparison group subjects. As such data were not available for non-participants, two different methods were adopted to assess possible participation bias.

The first method was a simple, general methodology in which the overall health status of Gulf War and comparison group non-participants was hypothesised, and an age-adjusted estimate, of the odds ratio that would have been observed in the complete sample, was

computed. A graphical display is presented to assess the sensitivity of conclusions to the hypothesised values of the non-participants' health status (for an example see Figure 6.1).

The second method used a series of probability models to impute (ie, predict) the health status of individual non-participants and to compute the odds ratio using the resultant "complete" data. As a stochastic mechanism (ie, random number generation) was used to perform the imputations, the imputation process was repeated multiple times. The average of the resulting odds ratios was taken as the estimate of the true odds ratio relating the health of Gulf War veterans and comparison group subjects. This procedure is an approximation of the statistical technique known as multiple imputation.[332] Details of both methods are presented in the sections that follow.

The interpretation of the results of the first method above, and the core of the modelling process for the second method above, rely on the utilisation of the physical (PCS) and mental (MSC) component summary scores of the SF-12 questionnaire as proxy measures of health status, available for the non-participants who completed the telephone questionnaire. Using these data, and under assumptions about the representativeness of the non-participants who completed the telephone questionnaire (see Section 6.3.2), it is possible to get an indication of the possible health status of all non-participants. This is achieved, in a broad sense, by examining differences in SF-12 scores across participants and telephone questionnaire subjects, and across study groups and broad age category (<25 versus ≥25 years in August, 1990). Note that age was chosen as a sub-grouping variable as it was clearly related to participation and is also associated with many health outcomes. Choosing a single cut-point to divide age into two categories makes presentation simpler and yet allows the control of this important confounding variable in assessments of differences in health outcome between Gulf War and comparison group subjects. The choice of the cut-point of 25 years for categorisation of age was made because 25 years was approximately the median age among telephone respondents. This cut-point therefore provided reasonable sample sizes in each category to facilitate numerical stability, in addition to separating low from high participation (see Table 6.5).

Table 6.7 Median SF-12 PCS and MCS scores for Gulf War veteran and comparison group participants and telephone questionnaire subjects across age categories

		Gulf War veterans			Comparison group		
Age		**N (% of non-participants)***	**Median PCS**	**Median MCS**	**N (% of non-participants)***	**Median PCS**	**Median MCS**
< 25	**Participants**	576	53.1	50.5	532	54.2	54.5
	Telephone	35 (19%)	53.6	56.8	145 (25%)	54.3	55.9
≥ 25	**Participants**	829	51.7	51.3	1021	52.4	53.9
	Telephone	40 (23%)	53.8	56.9	186 (30%)	53.8	55.9

* For telephone questionnaire-only subjects

The sample sizes for the participants and telephone questionnaire subjects, the percentage of total non-participants represented by the telephone questionnaire subjects, and the median SF-12 PCS and MCS scores are shown in Table 6.7 for the Gulf War veteran group and comparison group for each age category. Medians are presented as the PCS and MCS

distributions were found to be left skewed. The means displayed similar relationships but were uniformly lower in magnitude. For interpretation of the SF-12 scores, recall that higher SF-12 scores represent better self-reported health.

Previously it was shown that telephone questionnaire-only subjects recorded higher MCS scores than full participants in both study groups, but particularly so in the Gulf War veteran group (see Table 6.6). Table 6.7 demonstrates, in addition, that the difference in MCS scores between participants and telephone questionnaire subjects is reasonably consistent across age categories within the Gulf War and comparison groups. In the case of the PCS scores, the differences are uniformly less pronounced.

The health differential between telephone participants and full participants therefore appears to be unidirectional within each age stratum and within each study group, with telephone participants recording better mental heath than full participants in each age stratum and in both study groups. If the SF-12 measure is a valid proxy of health in participants and non-participants, then the health differential implies that the Gulf War veterans and comparison group non-participants will be of *better* health status than the participants in both of these groups. As a result, the overall prevalence of illness, combining all participants and non-participants, will be lower than that found for the participants alone. However, odds ratios, which represent the extent to which the prevalence of ill-health differs between the two study groups, may be over or underestimated according to the relative differences in health between the participants and non-participants in these groups. The examination of the effect of participation bias on odds ratios, using two methods, is presented in the following sections 6.4.1 and 6.4.2.

6.4.1 Method 1: Grouped data assessment of participation bias

The essence of the first method is to hypothesise the extent (via the prevalence) of ill-health among non-participants within each age category of the Gulf War and comparison groups. These hypothesised prevalences are then applied in order to obtain an overall age-adjusted odds ratio as if there had been complete participation from the outset. Note that no individual data are imputed in this method.

The methodology proceeds using concepts of Mantel-Haenszel estimation of a common odds ratio from a series of 2x2 tables.[333] Specifically, the hypothesised prevalences of ill-health among non-participants within each age category of the Gulf War and comparison groups are combined with the observed prevalences among the full participants to yield a "complete sample" prevalence within each age category. These are then combined by the Mantel-Hanszel method to estimate the overall "complete sample" odds ratio. The difference between this predicted "complete sample" odds ratio and the observed odds ratio among participants reflects the degree of participation bias in the observed odds ratio.

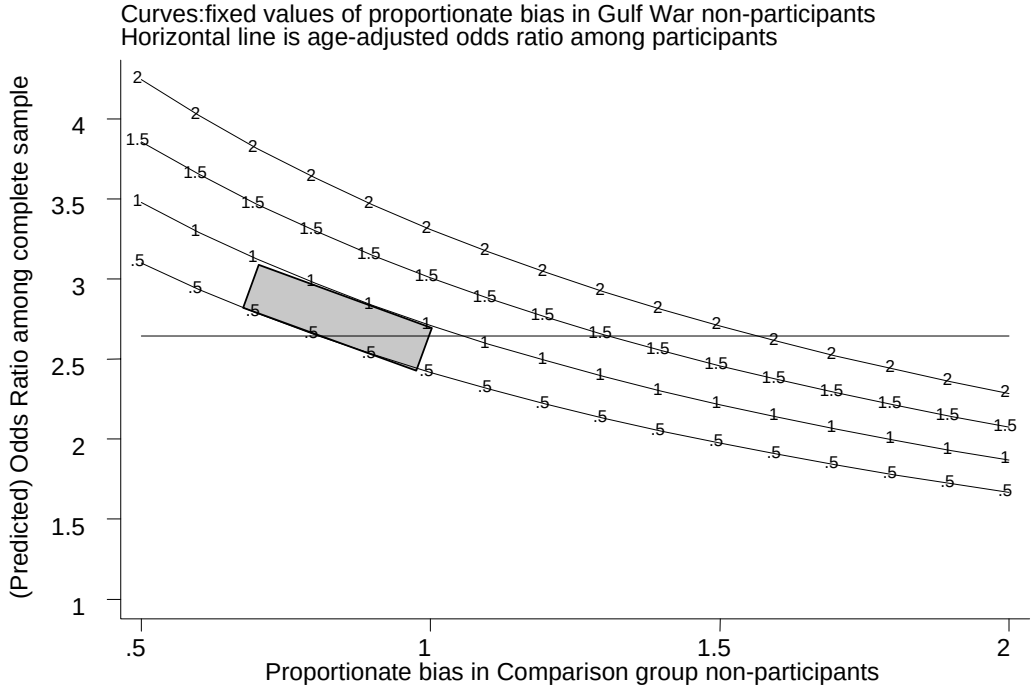
It is convenient to consider the prevalence of ill-health among non-participants via a ratio measure, proportionate to the participants, which we have called "proportionate bias". For example a proportionate bias value of 0.5 indicates that the prevalence of ill-health among non-participants of a certain study group age category (eg, Gulf War veterans aged <25 years), is half the prevalence of ill-health among the participants in the same study group and age stratum. Similarly a proportionate bias value of 2 indicates that the prevalence of ill-health among non-participants is twice that of participants in the same stratum.

For graphical presentation of results, it simplifies matters to constrain the two proportionate biases within the Gulf War group to be equal (ie, same proportionate bias for those aged <25 as for age >25), and to similarly constrain the two proportionate biases in the comparison

group to be equal. This reduces the presentation load from four participation bias parameters to two.

The following figure presents an example of predicted odds ratios for the complete sample according to the proportionate bias in the comparison group, at each of four fixed levels (0.5, 1, 1.5, 2) of proportionate bias in the Gulf War group. The data are the post-Gulf War CIDI defined anxiety disorder results from the Psychological Health chapter (see Chapter 11). No substantive interpretation of these results will be provided here as the data are for illustration only.

Figure 6.1 Predicted odds ratios for compete sample, at varying levels of proportionate bias in non-participants, where observed age-adjusted odds ratio is 2.6.



The prevalence of post-gulf anxiety in Gulf War veteran participants, aged <25, was 9.5% whereas in the comparison group it was 2.8%. Among those aged >25, the prevalence was 6.1% in the Gulf War group and 3.0% in the comparison group. This produces an age-adjusted (Mantel-Haenszel) odds ratio of 2.6, represented by the horizontal line in the Figure, meaning that the odds of the anxiety is reported to be 2.6 times higher in Gulf War participants than in comparison group participants within the same age stratum. The curved lines represent the fixed proportionate bias values (0.5, 1, 1.5 and 2) in Gulf War veteran non-participants.

Figure 6.1 demonstrates that the predicted odds ratio in the complete sample may vary between 1.7 and 4.2, albeit in rather unlikely scenarios. The value of 1.7 arises when the Gulf War non-participants have half the prevalence of anxiety as the Gulf War participants, and the comparison group non-participants have twice the prevalence of anxiety as the comparison group participants. In this case the observed odds ratio among participants is an overestimate of the odds ratio in the complete sample. Similarly the odds ratio of 4.2 arises at the opposite extreme when the non-participants in the Gulf War group have twice the

prevalence of anxiety as the participants, with the opposite being true for the comparison group.

Based on the demonstration that SF-12 MCS results displayed higher scores (ie, better health) for the telephone participants compared with full participants, and under the assumption that the telephone participants are representative of the health of the non-participants, the health of non-participants would be expected to also be better than that of the participants. It then follows that the proportionate bias within both groups would be expected to have values less than one. In this instance, the relevant section of Figure 6.1 to be examined would be the area between the curves labelled 0.5 and 1, and to the left of 1 on the horizontal axis. However, recalling that the difference between the SF-12 MCS scores of telephone participants and full participants was greater for Gulf War veterans than for comparison groups subjects, the proportionate bias for Gulf War veterans would, accordingly, be expected to be greater than that for comparison group subjects. This suggests that the relevant region on the horizontal axis (ie, comparison group proportionate bias axis) could be further constrained to be between approximately 0.7 and 1. This area is shaded in Figure 6.1 for convenient reference. The estimated complete sample odds ratios within this range vary from approximately 2.4 to 3.2, and these do not vary to a large degree from the observed odds ratio among full participants of 2.6. Observe also that it is possible for substantial proportionate bias to exist *within* each group, and yet the complete sample odds ratio need not be biased. For example, consider a proportionate bias of 0.50 in Gulf War veterans, and 0.80 in comparison group subjects; Figure 6.1 indicates that the predicted complete sample odds ratio is almost identical to the odds ratio among participants.

It should be noted, however, that the shaded region is only an approximation as the precise relationship between SF-12 scores and each health outcome among non-participants is not known and is postulated only generally here.

Other similar examples can be constructed. For example, an illness with a prevalence of approximately 7% among comparison group subjects and an odds ratio of 1.2 among participants would be expected to yield complete sample odds ratios between approximately 1.1 and 1.4 for proportionate biases in the range described in the previous example (ie, Gulf War veterans 0.50-1.0, comparison group 0.70-1.0). This range of proportionate biases does not indicate substantial participation bias in the odds ratio. Other examples demonstrate that the higher the prevalence for a given odds ratio among participants, the wider the variation in complete sample odds ratios.

6.4.2 Method 2: Individual data imputation-based assessment of participation bias

In this section we use the SF-12 data more directly than was the case with the grouped data method. In brief, the SF-12 data for full and telephone-questionnaire participants are used to generate predicted SF-12 responses for remaining non-participants. These predicted or imputed values are then used further to predict the broader health status of non-participants. The assumptions behind the procedure include being able to predict the SF-12 mental and physical health of non-participants using the relationship between SF-12 scores and deployment status, age, rank, service type and serving status that was observed among telephone-questionnaire participants. Furthermore, the health outcome of non-participants is assumed to be able to be predicted using the relationship between the health outcome and the above factors and SF-12 scores observed in full participants. Collectively, the missing data among non-participants are assumed to be "missing at random" given knowledge of all the observed data.[332] Technical details of the imputation methodology are contained in a Technical Supplement at the conclusion of this chapter (see Section 6.6)

Using the two-step modelling mechanism of first imputing SF-12 scores, followed by imputing the health status of non-participants, a "complete" dataset was formed. This "complete" dataset was then used to compute an odds ratio via logistic regression relating deployment status to the health outcome after adjusting for age, rank and service. The entire imputation procedure was then replicated 100 times. The average imputed odds ratio from the 100 replications represents the best estimate, based on the observed data and the imputation model for the health status of non-participants, of the true odds ratio underlying the relative health of Gulf War veterans and non-deployed subjects. The difference between the average imputed odds ratio and the actual observed odds ratio among participants reflects the degree of participation bias, and is the focus of this assessment.

As an example of the methodology, consider the post-Gulf War CIDI anxiety disorder data and the results from 100 replications of the imputation process:

Participants			Imputed results			
GWV prevalence	**Comp group prevalence**	**Odds Ratio**	**Average GWV prevalence**	**Average Comp group prevalence**	**Average Odds Ratio**	**Range**
8.3%	3.1%	2.77	7.5%	2.9%	2.68	1.95-3.71

Under the assumptions of the imputation model, the estimated true odds ratio is 2.68, which differs only slightly from the observed odds ratio of 2.77 among participants, indicating minimal participation bias. Note also that, as anticipated from the previous section, the imputed prevalence of post-gulf anxiety in either deployment group is lower than the corresponding prevalence among participants due to the more favourable SF-12 scores observed among telephone participants than full participants. More detailed discussion of this and other related health outcomes is deferred to the Psychological Health chapter (see chapter 11).

The imputation procedure described above relies upon the assumptions that the missing data are missing at random, and that the imputation models are correctly specified. The procedure is one, simplified application of a more general multiple imputation strategy. More comprehensive modelling and inference can be obtained using a variety of imputation models and more formal Bayesian inferential methods.[334] An advantage of the grouped data method for assessing participation bias described in the previous section over that of the individual data imputation method is that the former can be applied to a range of hypothesised values of the proportionate bias in each group and need not rely on the specification of statistical models. The fact that the odds ratios are only adjusted by a binary age variable, as opposed to a fuller set of adjustment factors, does not severely detract from the method's applicability. In fact, for most analyses described in this report, adjustment for further potential confounding factors had little impact on the results.

6.5 Discussion

Overall, more than 80% of Australia's 1808 recruitable Gulf War veterans, and more than 56% of the 2796 recruitable comparison group subjects participated either in full or by postal questionnaire in this study. Full participation included completion of both the postal questionnaire and medical assessment, and often participants undertook lengthy travel, sometimes requiring overnight accommodation, to attend a HSA clinic. The recruitment results compare very favourably with international survey-based studies where response rates have been from as low as 31% in a study of more than 16,000 active duty and reserve

personnel,[335] to as high as 95% in a study of 630 Gulf War veterans directly recruited at training sessions.[179] Table 6.8 contains a brief review of participation rates in international epidemiological studies. These studies have been primarily questionnaire-based surveys, with only one of these studies[162] including a medical examination as a component of the data collection.

The inability to locate subjects, particularly those who have left the armed services since the Gulf War, has proven to be a major factor affecting participation rates in many studies. Kang *et al* reported 90% participation by all located subjects but a participation rate of 70% among all eligible subjects,[20] and the Iowa Persian Gulf Study Group reported a 91% response rate amongst located subjects compared with their overall participation rate of 76%.[16] Despite multiple strategies employed to locate current contact details for all recruitable subjects in this study, more than 300 such subjects (7%) remained non-contactable upon closure of the recruitment period.

The reduced response rate amongst the comparison group, compared with the Gulf War veteran group, is consistent with other major epidemiological studies, which utilised a non-Gulf War comparison group. For example, Unwin *et al* reported response rates of 70.4% in their Gulf War cohort compared with 61.9% in their Bosnia cohort and 62.9% in their non-deployed control population.[21] Similarly, Ishoy *et al* reported participation rates of 83.6% in the Gulf War veteran group and 57.7% in the control population.[162]

Despite the findings of reduced participation rates amongst non-Gulf War comparison groups, few studies have formally evaluated participation bias in published papers. We investigated the issue of participation bias in several ways. Firstly, we were able to make some comparisons between all participants and all non-participants on a few parameters thought to influence health status. This analysis showed that younger people tended to be under-represented in the participating groups, as were those of lowest rank category. The difference in rank distribution is likely to be related to the aforementioned age differential. Secondly, the inclusion of the SF-12 Health Survey in the telephone questionnaire, administered to approximately one quarter of the non-participants, enabled us to compare participants with this subset of non-participants, on this health measure as well as other demographic and lifestyle factors. This investigation showed the most apparent difference between groups was in the Mental Component Summary score derived from the SF-12, indicating that participants had slightly poorer self reported mental health than non-participants.

Table 6.8: Participation rates in international epidemiological studies.

Study reference	Gulf War veterans	Non-Gulf War comparison groups	Study characteristics
	% Participation (total sample size)	% Participation (total sample size)	
Perconte *et al* 1993[179]	95% (620)	NA	Participants recruited during weekend training sessions. Data collected via questionnaire.
Cherry *et al* 2001[157]	85.1% (9505)	82.9% (4749)	Recruitment via mail, personal visit to Units, telephone contact and home visits. Data collected via questionnaire.
Ishoy *et al* 1999[162]	83.6% (821)	57.7% (400)	Postal questionnaire followed by health examination.
Wolfe *et al* 1998[159]	78.4% (2949)	NA	Participants recruited within five days of return to US. Data collected via questionnaire.
Iowa Persian Gulf Study Group 1997[16]	78.3% (2421)	73% (2465)	Telephone survey.
Kang *et al* 2000[20]	75% (15,000)	64% (15,000)	Data collected via postal questionnaire followed by telephone administered interview with non-respondents.
Southwick *et al* 1993, 1995[336, 337]	74.4% (160) at 1 mo 52.5% at 6 mo 38.8% at 2 yrs	NA	Participants recruited at training sessions at 1 mo, 6 mo and 2 yrs following return from Gulf. Data collected via questionnaire.
Goss Gilroy Inc., 1998[22]	73% (4262)	60.3% (5699)	Data collected via postal questionnaire.
Unwin *et al* 1999[21]	70.4% (4246)	Bosnia cohort: 61.9% (4250) Not deployed: 62.9% (4248)	Data collected via postal questionnaire.
Holmes *et al* 1998[338]	57.3% (517)	42.2% (497)	Data collected via postal questionnaire.
Haley *et al* 1997[158]	41% (606)	NA	Recruitment via mail and telephone. Data collected via self-administered questionnaire in supervised groups.
Stretch *et al* 1995[335]	31% (16,167)	NA	Recruitment and data collection via distribution of questionnaires through Units.

We explored the impact of varying magnitudes and directions of hypothesised non-participation bias upon the prevalence of ill-health and odds ratios likely to be found in this study. These computations, based on the telephone questionnaire results, showed that non-participation is likely to produce only a small bias in the observed odds ratios among full

participants. Therefore, participation bias is unlikely to explain large differences in measures of health, between the participating Gulf War veterans and comparison group subjects, in our study.

There are several limitations, however, to the use of telephone questionnaire results to predict health in non-participants, and to compare participants with non-participants. Firstly, the telephone questionnaire results may not be generalisable to the larger non-participant population. Telephone questionnaire subjects made up approximately one quarter of all comparison group non-participants and one fifth of all Gulf War veteran non-participants. It is not possible to determine whether the SF-12 scores of the telephone participants are similar, on average, to those of the remaining non-participants. Responses to the SF-12, and the relationship between those and variables such as study group, age and rank may not be predictive of accurate SF-12 scores in non-participants. Also, the relationship between participants' SF-12 scores and other health outcomes, such as psychological health outcomes, may not be predictive of the health outcomes of non-participants.

The direct comparison of telephone questionnaire derived mental health measures, with those derived from the self-administered postal questionnaire, should also be undertaken with some caution. There is some evidence to expect telephone questionnaire respondents to report improved mental health when compared with those completing self-administered questionnaires.[339-341] Therefore, improved SF-12 MCS scores among telephone questionnaire subjects in this study, when compared with participants who completed the SF-12 via the self-administered questionnaire, could partly be an artefact of the method of administration of the instrument.

In summary, participation rates in this study compared favourably with international studies, particularly considering the lengthy questionnaire, comprehensive medical assessment and, in many cases, lengthy travel undertaken by participants. Non-participation was highest in the comparison group, in the youngest subjects and in the lowest ranks. Despite some limitations, however, the inclusion of the telephone questionnaire proved a valuable tool for collecting brief, yet useful demographic, lifestyle and health information on a subset of non-participants and this data was used for an investigation of possible participation bias. It was concluded that whilst some health-related participation bias may exist, the magnitude and likely effects of this appear small, based both on the information drawn from the telephone questionnaire responses, and on predictions of health outcomes in non-participants derived from patterns observed in participants. Participation bias for some health outcome measures in this study remains, nonetheless, a possibility.

6.6 Technical Supplement – Details of the imputation procedure for non-participation

This Supplement describes the more technical details of the imputation procedure involved in the assessment of non-participation bias. The procedure consisted of two stages, reflecting the "monotone" missing data pattern, as described in Rubin (1987).[332] Data concerning deployment group, age, rank, service and serving status were available for all sampled persons; SF-12 mental and physical scores for full telephone participants; and comprehensive health outcome data for all full participants. The imputation procedure operated by first fitting a joint multiple linear regression model predicting SF-12 physical and mental health scores from deployment group, age, rank, service and serving status. All available data were used, together with a binary variable indicating full or telephone participant status, and a term for the interaction of the binary status indicator variable with deployment group. To reflect uncertainty in the model parameters, a random draw was made of these parameters from their posterior distribution given the observed data, and assuming a non-informative prior distribution. (In brief, and more simply put, a prior distribution summarises the information available about a parameter prior to observing a new set of data; the posterior distribution summarises the updated information about the parameter after observing the data.)[342] Predicted SF-12 scores were generated for non-participants using these sampled parameters and their deployment group, age, rank, service and serving status. A randomly generated normally distributed residual (with variance equal to a random draw from the posterior distribution of the residual variance from the linear regression) was then added to each predicted value to provide comparable variability of imputed SF-12 scores to that of the observed SF-12 scores.

The second step involved fitting a logistic regression model to the full participant data to predict the health outcome of individuals using their deployment group, age, rank, service, serving status and SF-12 scores as predictors. After drawing a value of the model parameters from their approximate posterior distribution (obtained from large sample maximum likelihood theory), predicted probabilities of the health outcome were generated for each non-participant based on their observed values and their imputed SF-12 scores (or observed SF-12 scores for telephone participants). Finally, the actual health status of each individual was imputed by generating a uniform random number and comparing it to the predicted probability for each individual. In this manner a "complete" data set was formed.

Note that the imputation procedure was implemented for binary health outcomes only. In addition, adjustment in the final logistic regression model was made for age, rank and service type only, as these were the key confounding variables that were available for all participants. Adjustment for other variables (eg, education level) would have required additional imputation, which was considered undesirable and therefore was not implemented.

7. Demographic, socioeconomic and lifestyle factors

7.1 Aims

The aim of this analysis is to:

- present a descriptive profile of the participating men in the Gulf War veteran group and comparison group,
- assess these two study groups for differences in demographic, socioeconomic or smoking or alcohol consumption patterns, which may impact upon the results of the health investigations.

All results in this chapter refer to male participants. The information in relation to female participants is presented in chapter **15** All results for female participants have been presented separately from those of male veterans because the numbers of females are quite small and health patterns in men and women can be quite different. If the data for the female participants was included with the male data, patterns specific to women would be difficult to identify.

7.2 Research questions

1. Are Australian Gulf War veterans similar to the comparison group in relation to demographic factors, including age and ADF service related parameters?

2. Are Australian Gulf War veterans similar to the comparison group in relation to socioeconomic factors, including educational and occupational status?

3. Are Australian Gulf War veterans similar to the comparison group in relation to lifestyle factors, particularly tobacco smoking and alcohol consumption?

7.3 Methods and materials

7.3.1 Subjects

Subjects included in this analysis were all males who completed the self-administered postal questionnaire. These included 1424 Gulf War veterans and 1548 comparison group subjects.

7.3.2 Measurement of demographic and socioeconomic variables

Demographic variables including age, country of birth, indigenous status, language spoken at home and marital status were collected by postal questionnaire.

Information in relation to ADF service type at August 1990, and ADF employment status at time of sampling (serving versus not serving), was provided by the DVA. All other socioeconomic measures, including the ADF-related parameter 'Rank at Jan 1991', highest level of education, occupational status, periods of unemployment three months or greater since August 1990, and main source of income were self-reported in the postal questionnaire.

Responses to the parameter "Rank at Jan 1991" were used to categorise subjects in to the following groups:

- Officers: This group included all commissioned officer ranks.
- Other ranks – supervisory: This group included all non-commissioned officer ranks and junior non-commissioned officer ranks. These ranks are considered to hold supervisory

positions in the three services. The lowest ranks included, in this category, were Leading Seaman in the Navy, and Corporal in the Army and Air Force.

- Other ranks – non supervisory: This group included the remaining enlisted ranks; Seaman and Able Seaman in the Navy, Private and Lance Corporal in the Army, and Aircraftman/Aircraftwoman and Leading Aircraftman/Aircraftwoman in the Air Force.

7.3.3 Measurement of cigarette smoking and tobacco use

Smoking status and total pack-years of cigarette consumption, for current and former smokers, were derived from responses to a brief set of questions in the postal questionnaire. Participants were categorised in to three 'smoking status' categories similar to those used by the Australian 2001 National Drug Strategy Household Survey.[343]

Current smoker: Subject had smoked at least 100 cigarettes in his life-time and currently smoked at least one cigarette per day or one cigar per week or one ounce of tobacco per month.

Former smoker: Subject had smoked at least 100 cigarettes in his life-time, did not currently smoke at least one cigarette per day or one cigar per week or one ounce of tobacco per month, but had smoked as much as this in the past.

Never/occasional smoker: Subject had never smoked as much as one cigarette per day or one cigar per week or one ounce of tobacco per month.

For the purpose of calculating total pack years of cigarette consumption, for current and former smokers, it was necessary to derive the total duration, in years, of cigarette consumption and the average number of cigarette-packs, or equivalent, smoked on each day of those years.

Current and former smokers were asked to report the age at which they first started smoking regularly, and former smokers were asked to report the age at which they stopped smoking regularly. Years of smoking were calculated as the period elapsed between the age of first regular smoking and current age (for current smokers) or age last smoked regularly (for former smokers).

Smokers were asked to provide an estimate of the average number of cigarettes smoked daily, the average number of grams of tobacco smoked daily (not including tobacco from cigarettes or cigars) and the average number of cigars smoked weekly.

The information on years of smoking and average number of cigarettes daily was used to calculate the total number of cigarettes smoked, and this was expressed in pack-years. It was assumed that one pack contained 20 cigarettes, that one cigar was equivalent to three cigarettes[1] and that one gram of tobacco was equivalent to 2 cigarettes[2]. Pack-years were calculated as = total cigarettes (or equivalent) ÷ 20 ÷ 365. One pack year is equivalent to smoking one pack of 20 cigarettes per day for a year. A person who smoked an average of 16 cigarettes per day for a duration of 12 years (the equivalent of 70,080 cigarettes) received a pack-years score of 9.6 (70,080 ÷ 20 ÷ 365 = 9.6).

[1] Estimate based on the American Cancer Society report (344. American Cancer Society. Cigar smoking and cancer: Is cigar smoking on the rise? Atlanta, Georgia: American Cancer Society, 2000.) which indicated that "Most cigars have as much nicotine as several cigarettes"

[2] Estimate based on King & Borland (345. King R, Borland R. The growth of 'low tar' and ventilated filter cigarettes in Australia. *Nicotine and Tobacco Research* submitted.) who gave the median tobacco weight for Australian cigarettes as 536 milligrams

7.3.4 Measurement of alcohol consumption

The pattern and level of alcohol consumption was derived from postal questionnaire responses to the first three questions of the Alcohol Use Disorders Identification Test (AUDIT).[276] These questions covered frequency of alcohol consumption, average number of standard drinks on a typical day when drinking and frequency of drinking six or more alcoholic drinks on one occasion of drinking.

7.4 Results

7.4.1 Demographic and socioeconomic variables

Table 7.1 shows the mean age of male Gulf War veteran and comparison group participants and the numbers and percentages of participants within sub-categories of the various demographic and socioeconomic parameters measured.

It should be noted that the variable 'age', in this descriptive table, is age at the time of participation in the study. This is in contrast to the previous Recruitment chapter where age at August 1990 (the time of the start of the Gulf War) was used to compare participants with non-participants.[3] Further, the parameter "Rank in January 1991" reported in Table 7.1 is drawn from postal questionnaire responses, in contrast to the parameter "Rank in August 1990" which was reported in the Recruitment chapter for all participants and non-participants, and which was sourced from DVA records.[3]

On average, male Gulf War veterans were approximately one year younger than male comparison group participants, less highly ranked in January 1991 and less likely to have tertiary education. Gulf War veteran Army and Air Force males were less likely to participate than comparison group males of these service types, and Gulf War veteran Navy males were more likely to participate than their comparison group counterparts. These differences reached statistical significance.

Male participants of both groups were equally likely to be born in Australia, to speak English as the main household language, to be married, to be in paid employment and to be sourcing their main income from a wage or own-business. Gulf War veterans and comparison group participants reported similar levels of indigenous origin, however large numbers of subjects in both groups (> 7%) failed to respond to this question. Approximately two thirds of subjects in each group were no longer serving members of the ADF at the time of sampling.

Gulf War veterans were no more likely, than the comparison group, to have sustained a period of unemployment of three months or greater since August 1991. However the Gulf War veteran participants were more likely to report that such a period of unemployment was primarily health related.

[3] Wherever possible self reported sources of data are used for the comparison of participating groups in this report. In the recruitment chapter, self reported data was often not available for non-participants, and therefore data sourced from DVA records was often used for comparisons of participants with non-participants.

Table 7.1 Demographic and socioeconomic parameters for male Gulf War veteran and comparison group participants

Demographic and socioeconomic parameters	Gulf War veterans (N=1424)		Comparison group (N=1548)		
	Mean	**(SD)**	**Mean**	**(SD)**	**P value**
Age at date of participation	38.1	(6.4)	39.3	(6.4)	<0.001
	n	**(%)**	**n**	**(%)**	**P value**
Age category at date of participation					
<30	114	(8.0)	62	(4.0)	
30-34	413	(29.0)	386	(24.9)	
35-44	689	(48.4)	796	(51.4)	<0.001
≥45	208	(14.6)	304	(19.6)	
Service type at Aug 1990					
Navy	1232	(86.5)	1123	(72.5)	
Army	87	(6.1)	172	(11.1)	<0.001
Air Force	105	(7.4)	253	(16.3)	
Rank at Jan 1991					
Officer	268	(18.8)	391	(25.3)	
Other rank-supervisory	686	(48.2)	740	(47.8)	<0.001
Other rank-non supervisory	468	(32.9)	417	(26.9)	
ADF employment status					
Serving	605	(42.5)	624	(40.3)	
Not-serving	819	(57.5)	924	(59.7)	0.229
Country of birth					
Australia	1194	(83.8)	1289	(83.3)	
UK/Ireland	148	(10.4)	177	(11.4)	
New Zealand	14	(1.0)	20	(1.3)	0.589
Other	64	(4.5)	61	(3.9)	
Aboriginal or Torres Strait Islander					
Yes	19	(1.3)	22	(1.4)	
No	1301	(91.4)	1405	(90.8)	0.825
Missing	104	(7.3)	121	(7.8)	
Language usually spoken in household					
English	1406	(98.7)	1531	(98.9)	
Other	6	(0.4)	3	(0.2)	0.260
Marital status					
Married/defacto	1080	(75.8)	1195	(77.2)	
Separated/divorced/widowed	162	(11.4)	187	(12.1)	0.223
Single, never married	171	(12.0)	156	(10.1)	

Demographic and socioeconomic parameters	Gulf War veterans (N=1424)		Comparison group (N=1548)		
Highest education level					
Up to year 10	266	(18.7)	273	(17.6)	
Years 11 or 12	264	(18.5)	225	(14.5)	
Certificate or Diploma	694	(48.7)	772	(49.9)	0.002
Tertiary	196	(13.8)	274	(17.7)	
Occupational status					
Paid employment (FT, PT, self-employed)	1309	(91.9)	1440	(93)	
Not working due to ill-health	29	(2.0)	26	(1.7)	
Unemployed	45	(3.2)	41	(2.6)	0.653
Other (student/volunteer/home-duties/retired)	39	(2.7)	37	(2.4)	
Any period of unemployment more than 3 months since august 1991					
Yes, primarily due to health problems	75	(5.3)	52	(3.4)	
Yes, not primarily due to health problems	229	(16.1)	283	(18.3)	0.015
No	1102	(77.4)	1202	(77.6)	
Main income source					
Wage/own business	1298	(91.2)	1421	(91.8)	
Disability pension	22	(1.5)	20	(1.3)	
Other Govt pension or allowance	65	(4.6)	58	(3.7)	0.356
Superannuation/dividends	29	(2.0)	43	(2.8)	

7.4.2 Cigarette smoking and tobacco use

The breakdown of male Gulf War veteran and comparison group participants according to smoking status, and means and standard deviations (SD) for total pack-years for current smokers and former smokers, are shown in Table 7.2. The proportions of subjects who were categorised as current, former or never/occasional smokers were similar in the two study groups. Gulf War veteran current smokers and former smokers, however, averaged fewer pack-years of smoking when compared with comparison group current smokers and former smokers.

7.4.3 Alcohol consumption

Responses to the alcohol frequency and quantity questions of the AUDIT, for Gulf War veteran and comparison group participants, are presented in Table 7.3. Patterns of alcohol consumption were very similar in the two groups.

Table 7.2 Smoking status for male Gulf War veteran and comparison group participants, and mean total pack years for current smokers and former smokers.

Smoking	Gulf War veterans		Comparison group		
	n	(%)	n	(%)	P value
Smoking status					
Current smoker	369	(25.9)	356	(23.0)	0.172
Former smoker	433	(30.4)	498	(32.2)	
Never/occasional	619	(43.5)	690	(44.6)	
Cigarette pack years	**Mean**	**(SD)**	**Mean**	**(SD)**	**P value**
Current smokers	18.5	(14.9)	21.6	(18.2)	0.012
Former smokers	12.6	(13.5)	14.9	(17.8)	0.027

Table 7.3 Frequency and quantity of alcohol consumption for male Gulf War veteran and comparison group participants.

Alcohol	Gulf War veterans		Comparison group		
	n	(%)	n	(%)	P value
Frequency of taking a drink					
Never	45	(3.2)	43	(2.8)	0.901
Once a month or less	169	(11.9)	178	(11.5)	
2 to 4 times per month	391	(27.5)	434	(28.0)	
2 to 3 times per week	454	(31.9)	511	(33.0)	
4 or more times per week	361	(25.4)	379	(24.5)	
Amongst drinkers: number of drinks on a standard day					
1 or 2	490	(35.6)	559	(37.2)	0.318
3 or 4	462	(33.6)	521	(34.7)	
5 or 6	237	(17.2)	257	(17.1)	
7 to 9	94	(6.8)	89	(5.9)	
10 or more	89	(6.5)	74	(4.9)	
Amongst drinkers: frequency of taking 6 drinks or more on one occasion					
Never	152	(11.1)	195	(13.0)	0.181
Less than once a month	596	(43.3)	668	(44.5)	
Monthly	301	(21.9)	326	(21.7)	
Weekly	269	(19.6)	262	(17.4)	
Daily or almost daily	55	(4.0)	45	(3.0)	

7.5 Discussion

Demographic and socioeconomic parameters such as age, education level and marital status, and lifestyle factors such as smoking and alcohol consumption, are known predictors of health status. Amongst Australian adults younger age has been shown to be related to poorer mental health, as have lower education levels, whilst marriage has been shown to be associated with better mental health.[309] Health problems associated with alcohol consumption include liver damage, cancers, pancreatitis, diabetes and epilepsy. Alcohol is also a significant factor in motor vehicle injuries and fatalities, falls, drowning and suicide. Tobacco smoking has been associated with diseases including cardiovascular diseases, cancers, emphysema, stroke and thrombosis.[346] Differences in the health status of the Gulf War veteran and comparison group participants, unrelated to the deployment to the Gulf War, could result if these two study groups were markedly different in their demographic, socioeconomic and lifestyle patterns.

The comparison of the two groups in this study showed reassuring parallels in current smoking status and alcohol consumption, country of birth, indigenous origin, language spoken at home, marital status, ADF serving status, occupational status and main source of income. There were small differences between the two groups in relation to age, education level and rank at January 1991 and these could exert some confounding influence on the results of health outcome measures. Where possible, these differences will be statistically controlled for when the results of health outcome measures are assessed in the following chapters.

The different service-type pattern between the two groups could also exert some confounding effects upon the study health outcomes. Anecdotal evidence suggests that Army Gulf War veterans, particularly those who deployed with Operation Habitat, may have experienced poorer health than Gulf War veterans of the Navy and Air Force. In addition it would seem likely that Air Force participants, particularly air-crew personnel who are required to maintain a high level of health and fitness, would report improved health when compared with participants from other services. Any confounding effects of service type, however, are likely to be minor considering the relatively small numbers of contributing participants from the Army and Air Force services. Nevertheless, the true effects of service type will be considered carefully in the further analysis of health outcomes in this study.

Patterns of alcohol use could be considered both predictive of ill-health, and also a health outcome in itself. For example, stressful life events can be associated with the subsequent onset of heavy drinking.[347] Therefore, a more thorough investigation of alcohol use and alcohol related disorders will be presented in chapter 11.

Smoking patterns in both groups were very similar to those reported for the Australian male adult population in the 2001 National Drug Strategy Household Survey.[343] The pack-years difference between the two groups may be important and could imply poorer health in the comparison group related to this higher exposure. It must be noted however, that the pack-years estimates were based on years of smoking derived from reports of age first started smoking and year last smoked, with no reports of any remission from smoking for any intervening period. Whilst this method of recording years of smoking is recommended in the Australian National Health Data Dictionary,[348] it is likely to result in an overestimation of total pack-years in both groups.

Study participants were more likely to be Australian born, or British or Irish born, when compared with the average Australian, and more likely to be married.[349] Compared with the national average of 2%, study participants were less likely to be of indigenous

origin.[349]however the participation rate in this group is consistent with estimates that the Australian indigenous population comprises approximately 1.2% of total Australians in employment.

More than 40% of all male participants drank “six or more drinks on one occasion” on a monthly or more frequent basis. It is possible that a large proportion of these could be considered as regularly drinking in excess of the Australian NHMRC drinking guidelines for men, which includes the recommendation of “not more than 6 standard drinks in any one day”.[350] Our method of data collection, however, does not allow us to make a direct comparison with the NHMRC guidelines.

In conclusion, male participants in the two study groups were very similar with regard to many of the demographic and socioeconomic measures, and with regard to current smoking status and alcohol consumption patterns. Where differences were found in age, rank and education pattern these were typically small. In general it is unlikely that small differences between the two groups would exert considerable confounding influence upon the results of health investigations in this study. Increased pack year estimates amongst comparison group subjects may be associated with some increased morbidity in this group. However, the true influence of these factors, along with that of other possible confounding exposures unrelated to the Gulf War deployment, will be examined in more detail in subsequent chapters.

7.5.1 Summary of findings

In summary, and in relation to the research questions posed for this chapter:

Australian male Gulf War veterans and comparison group participants were very similar in relation to most demographic, socioeconomic and lifestyle measures, including current smoking status and alcohol consumption, country of birth, indigenous origin, language spoken at home, marital status, ADF serving status, occupational status and main source of income.

There were some differences between the two study groups in age, rank, service type, education and pack years of smoking. Whilst it is unlikely that these small differences will exert considerable confounding influence on the results of the study, where possible, statistical adjustment for these factors will be made.

8. Reported Gulf War and other exposures

One of the aims of our study is to investigate the relationship between excess risks of any physical and psychological health outcomes and Gulf War related exposures and experiences. To do this we need to investigate not only those exposures and experiences related to the Gulf War but also other exposures and experiences in military and civilian life which may influence health outcomes.

This chapter presents the exposures and experiences self-reported by male Gulf War veterans in relation to the Gulf War deployment, and by male participants in both study groups in relation to other active deployments, other military postings and any civilian occupations.

Also presented, are our methods of using the exposures and experiences data reported by Gulf War veterans to develop metrics of exposure. These metrics will be used to identify subgroups of Gulf War veterans in subsequent chapters to investigate associations between exposure types and health outcomes.

8.1 Aims

The primary aim of this analysis is to describe those service and exposure characteristics of male Gulf War veterans which may be related to health outcomes. Specifically the analysis aims to describe some service characteristics such as service type and operation, and the nature and extent of self reported preventive medical interventions, psychological stressors and chemical and environmental exposures reported by male Gulf War veterans in relation to their Gulf War deployment. The selection of these exposures and experiences has been guided by the literature review of Gulf War exposures in chapter **3**.

A secondary aim is to use Gulf War related exposure information to identify exposure categories in Gulf War veterans, and to identify subgroups of Gulf War veterans according to exposure type and level, for use in other analyses.

A final aim is to describe the exposures of Gulf War veterans and the comparison group in relation to other active deployments, military postings and any civilian occupations to assess important differences in the nature of the Gulf War deployment.

8.2 Research questions

1. What chemical and environmental exposures, psychological stressors, immunisations and preventive medications do Australian Gulf War veterans report experiencing in relation to the Gulf War?
2. Is the reporting of chemical and environmental exposures or psychological stressors related to age, rank or service type?
3. Do Australian Gulf War veterans differ from the comparison group with respect to their number of active deployments other than the Gulf War?
4. Are Australian Gulf War veterans and comparison group subjects similar in relation to their chemical and environmental exposures and psychological stressors experienced outside of the Gulf War?

8.3 Results

8.3.1 Service characteristics of the Gulf War deployment

Table 8.1 presents numbers of male Gulf War veterans according to several service characteristics of the Gulf War deployment. Most of the data were drawn from self-reported information except for deployment dates, which were drawn from the DVA Nominal Roll for the Gulf War conflict and were used to determine which Gulf War veterans completed their deployment(s) before or after the commencement of the air war on 17th January 1991 and subsequent ground war.

About one quarter of veterans had completed their deployment before the air war started. There were almost four times as many veterans deployed to frigates or destroyers compared to the numbers deployed to supply ships. About half of the Army veterans were on Operation Habitat.

Table 8.1 Male Gulf War veterans grouped by service characteristics

Metric	n	(%)
Service Type		
Navy	1232	(86.5)
Army	87	(6.1)
Air Force	105	(7.4)
Total	1424	(100)
Type of Ship		
Supply ship	236	(20.3)
Frigate or destroyer	929	(79.7)
Total	1165	(100)
Army		
Operation Habitat	43	(50.6)
Other Army, not Operation Habitat	42	(49.4)
Total*	85	(100)
Gulf War deployment completed before air war started (Jan 17th 1991)		
Yes	331	(23.3)
No	1092	(76.7)
Total	1423	(100)

*Two Army veterans did not indicate whether or not they were on Operation Habitat

Further ship and service groupings are shown in Table 8.2 along with some specific primary duties reported by Gulf War veterans in those subgroups.

Some Army personnel deployed with ships and are included in the ships' numbers. The Task Group Medical Support Elements deployed to United States Naval Ship (USNS) *Comfort* were made up of mainly Navy personnel but included Army and Air Force personnel. Operation Habitat was mainly Army. Most veterans identified the name and type of ship that they were on, but did not indicate whether they were involved in any of the other specific duties listed on the postal questionnaire. Relatively few veterans identified combat or combat

support as their primary duty, but most of those who did were deployed with Damask II. Most veterans who were primarily engaged in medical and environmental health duties were deployed to USNS *Comfort* or were on Operation Habitat. Almost all of the Air Force veterans stated that they were aircrew on transport duties, some of whom evacuated civilians. Most of the veterans classified as 'Other Navy' or 'Other Army' were on logistic support staff duties or a range of other activities but were not attached to ships. There were no veterans who reported being on submarines.

Veterans can be divided into groups on the basis of the service type, individual ship, and type of ship or date of completion of their deployment. These groups will predict exposure to some extent, but there will have been considerable intra-group variation for individual exposures and experiences. The exposures experienced by veterans on ships, for example, will differ for those who spent their time primarily above, or primarily below decks. Army veterans on Operation Habitat will have experienced different exposures to those Army veterans deployed on a ship or those carrying out support staff duties.

Table 8.2 Gulf War veterans sub-grouped by Operation, by ship in which they deployed, other service characteristics and by self reported primary duties during Gulf War

Groups	Total Numbers	Specific primary duties reported during the Gulf War*								
		Mine counter measures	Medical	Environmental health	Ground Crew	Airbase support	Combat support†	Engaged in combat‡	Logistic support staff duties	Other
Damask I										
HMAS *Darwin*§	188	4	2	1	2	1	19	12	3	21
HMAS *Adelaide*	148	2	3	0	2	0	9	5	8	14
HMAS *Success*	173	3	6	2	2	0	17	4	10	15
Damask II										
HMAS *Sydney*	192	2	8	2	1	0	30	28	11	20
HMAS *Brisbane*	300	11	8	0	0	3	54	30	11	19
HMAS *Westralia*	63	3	2	1	0	0	2	3	7	9
Damask III										
HMAS *Darwin*§	156	4	3	1	1	1	28	9	3	19
Clearance Divers§	19	18	1	1	0	0	0	1	0	12
USNS *Comfort*	33	0	31	0	0	0	2	0	1	11
Operation Habitat§	55	0	21	13	1	0	3	0	16	16
Other Army¶	21	0	0	0	0	1	4	5	7	10
Other Air Force¶	93	0	0	0	6	7	9	6	12	65
Other Navy¶	55	19	1	1	1	1	1	2	27	19

* Veterans can appear in more than one duty category
† Including flight-line support and convoy protection
‡ Including combat missions and combat patrols
§ 59 veterans served on HMAS *Darwin* in both Damask I and Damask III. 9 veterans are reported being on a ship and also serving in Op Habitat. 6 veterans are included as being on a ship and are also listed as clearance divers.
¶ Not included elsewhere, for example does not include Army personnel who were deployed in ships or on Operation Habitat

8.3.2 Other active deployments

Participation in active deployments, other than the Gulf War, were self-reported by participants in the postal questionnaire. Active deployments were defined as war or peacekeeping deployments and these specifically excluded training exercises or 'goodwill' visits. To facilitate accurate reporting of active deployments, participants were provided with a list of 26 active ADF deployments in recent history from which to choose. Participants could nominate additional active deployments which were not included on the list. These were checked by the study team and deployments in peaceful regions such as New Zealand, Canada and USA were excluded.

Table 8.3 presents those Gulf War veterans and comparison group subjects who reported involvement in one or more active deployment other than the Gulf War deployment. These represented 44% of the Gulf War veterans and 33% of the comparison group. Gulf War veterans (16.5%) were more likely than the comparison group (12.4%) to have been deployed on more than one other deployment.

Table 8.3 Active deployments (other than the Gulf War) for Gulf War veterans and comparison group subjects

Number of other active deployments	Gulf War veterans		Comparison group	
	n	(%)	n	(%)
Ever on active deployment	625	(43.9)	514	(33.2)
On 1 active deployment	390	(27.4)	321	(20.7)
On 2 active deployments	133	(9.3)	118	(7.6)
On 3 active deployments	69	(4.8)	44	(2.8)
On 4 or more active deployments	33	(2.3)	31	(2.0)

Table 8.4 identifies the active deployments in which Gulf War veterans and comparison group subjects reported having been involved in. These are ordered in decreasing frequency, as reported by Gulf War veterans. The most common deployments reported were those to the Gulf region but outside the time period used to define the Gulf War for the purposes of our study. The next most common deployments were to East Timor, to the Solomon Islands and to Bougainville (New Guinea). The most common deployments nominated in the category presented as 'Other', were to the Gulf of Oman and North West Indian Ocean in the early 1980s and to the Red Sea between 1991 and 1993. Gulf War veterans were more likely than the comparison group to have deployed to the Gulf region outside the time of the Gulf War. In relation to other active deployments, the two groups were similar.

Table 8.4 Non-Gulf War active deployments reported by Gulf War veterans and comparison group subjects

Active Deployments:	Gulf War veterans		Comparison group	
	n	(%)	n	(%)
Gulf (not between 2/8/90 & 4/9/91)	146	(10.3)	85	(5.5)
East Timor 1999 →	141	(9.9)	135	(8.7)
Solomon Islands	64	(4.5)	52	(3.4)
Bougainville 1997 →	63	(4.4)	54	(3.5)
Vietnam	50	(3.5)	53	(3.4)
Malaysia	41	(2.9)	73	(4.7)
Egypt	37	(2.6)	13	(0.8)
Somalia 1994	36	(2.5)	41	(2.6)
Southern Ocean	30	(2.1)	16	(1.0)
Cambodia 1993 -1999	25	(1.8)	16	(1.0)
Sinai 1982-1986 & Sinai 1993 →	25	(1.8)	22	(1.4)
Kuwait 1998 →	19	(1.3)	13	(0.8)
Papua New Guinea 1997-1998	19	(1.3)	19	(1.2)
Middle East 1956 →	12	(0.8)	13	(0.8)
Thailand	12	(0.8)	12	(0.8)
Gulf of Oman 1999	11	(0.8)	1	(0.1)
Rwanda	9	(0.6)	6	(0.4)
Namibia 1989-1990	6	(0.4)	3	(0.2)
Korea 1953 →	4	(0.3)	1	(0.1)
Afghanistan	2	(0.1)	3	(0.2)
Balkan's	2	(0.1)	4	(0.3)
Operation Relex	2	(0.1)	4	(0.3)
Former Rep of Yugoslavia 1997 →	1	(0.1)	2	(0.1)
Western Sahara	1	(0.1)	5	(0.3)
Angola	0	(0.0)	1	(0.1)
Mozambique 1994 →	0	(0.0)	2	(0.1)
Other*	217	(15.2)	136	(8.8)

* Reported deployments to regions such as New Zealand, North America or northern European countries (except Northern Ireland) were excluded.

8.3.3 Immunisations and preventive medications reported for the Gulf War deployment

Immunisations (referred to as vaccinations in the postal questionnaire) and preventive medications were reported in the postal questionnaire by Gulf War veterans in relation to their Gulf War deployment. Gulf War veterans estimated the numbers of immunisations received, the time period over which they received those immunisations (eg all in one session, across 1 week, across 2-4 weeks or over a period longer than 4 weeks) and whether those immunisations were received before deployment to the Gulf and/or in transit to the Gulf and/or while in the Gulf.

In relation to preventive medications, Gulf War veterans reported any use of anti-nerve agent pills including pyridostigmine bromide (NAPS), antimalarial tablets or anti-biological warfare tablets including ciprofloxacin or ciproxin.

Table 8.5 shows the estimated numbers of immunisations received by Gulf War veterans as part of their Gulf War deployment. Eight percent of veterans reported receiving no immunisations and 24% reported that they did not know how many immunisations they had received. The median estimated number of immunisations was six with the range being from 0 to 21 immunisations.

Veterans who had their WHO vaccination books reported higher numbers of immunisations than subjects who did not have their vaccination books. They were also less likely to report that they had not received any immunisations.

Table 8.5 Total number of immunisations reported by Gulf War veterans

	Total number of immunisations received							
	Don't know		No immunisations		1-5 immunisations		>5 immunisations	
	n	(%)	n	(%)	n	(%)	n	(%)
All Subjects (N=1418)	342	(24.1)	119	(8.4)	398	(28.1)	559	(39.4)
Subjects with WHO vaccination books (n=726)	75	(10.3)	35	(4.8)	252	(34.7)	364	(50.1)
Subjects without WHO vaccination books (n=692)	267	(38.6)	84	(12.1)	146	(21.1)	195	(28.2)

Veterans who reported receiving clusters of immunisations, defined as more than five immunisations within a period of one week or less, are shown in Table 8.6. These were sub-divided into those veterans reporting clusters of immunisations received before deployment to the Gulf, and those reporting clusters of immunisations received in transit to the Gulf or while they were in the Gulf.

Table 8.6 Gulf War veterans reporting clustered immunisations (>5 immunisations within one week or less)

	Gulf War veterans reporting clustered immunisations	
	n	(%)
Total (N=1113)	151	(13.6)
Before deploying to the Gulf	113	(10.2)
In transit to/while in the Gulf	35	(3.2)

Almost 14% of Gulf War veterans reported receiving immunisations in clusters. Three quarters of these veterans reported receiving these clusters of immunisations before deployment to the Gulf, whilst one quarter reported receiving them in transit to or when they were in the Gulf.

From a provided list of types of immunisations, Gulf War veterans reported which ones they believed they had received as part of the Gulf War deployment. The results are shown in Table 8.7. For almost all listed immunisations, more than 30% of the veterans did not know whether they had received them or not. More than 60% of veterans believed they had received immunisations for typhoid, cholera, and hepatitis B. Almost 50% believed that they had been immunised against plague but a further 38% were unsure. 15% reported immunisation against anthrax but 58% were unsure.

The receipt of anthrax immunisation was analysed by ship. Between 3.6% and 7.9% of veterans who deployed to USNS *Comfort*, and on Damask I and III reported receiving anthrax immunisation. However, a higher percentage of veterans who deployed with Damask II reported receiving anthrax immunisation, 14.2 to 28.1%. The highest percentage (28.1%) reporting receipt of anthrax immunisation was for veterans on HMAS *Brisbane*.

Table 8.7 Individual immunisations reported by Gulf War veterans

	Immunisations received		
Type of immunisation	**Yes**	**No**	**Don't know**
	n (%)	**n (%)**	**n (%)**
Hepatitis B	903 (66.0)	87 (6.4)	379 (27.7)
Typhoid	861 (63.3)	85 (6.3)	414 (30.4)
Cholera	849 (62.4)	68 (5.0)	444 (32.6)
Plague	641 (48.1)	185 (13.9)	507 (38.0)
Diphtheria, Tetanus (ADT)	465 (36.0)	266 (20.6)	560 (43.4)
Polio (oral Sabin)	407 (31.5)	304 (23.5)	581 (45.0)
Hepatitis A (Havrix)	312 (24.7)	309 (24.4)	643 (50.9)
Anthrax	192 (15.3)	331 (26.3)	736 (58.5)
Tuberculosis (BCG)	189 (15.2)	393 (31.6)	660 (53.1)
Smallpox	130 (10.5)	401 (32.2)	713 (57.3)
Measles, Mumps, Rubella (MMR)	89 (7.2)	430 (34.8)	716 (58.0)
Pertussis	60 (4.9)	415 (33.8)	752 (61.3)
Any other	155 (13.5)	236 (20.6)	753 (65.8)

More than half of the veterans who answered the questions about preventive medications believe they took NAPS, less than half believe they took antimalarials and almost 6% believe they took anti-biological warfare tablets (Table 8.8). Not all veterans who reported taking the NAPS or anti-biological warfare tablets provided sufficient information regarding quantity or duration to allow the total numbers to be calculated. Of the 456 subjects who did provide information about the quantity of NAPS taken, one third had taken more than 180 pills over the course of their deployment. If the tablets were taken at the recommended dose of one tablet three times per day, 180 pills equate to taking the tablets for a total duration of 2 months. A surprisingly high number of veterans, 38% were unsure of whether they had taken

antimalarials. More than half did not know whether they had taken anti-biological warfare tablets.

Approximately 13% of veterans (n=179) reported having a 'significant' reaction to an immunisation or medication (data not shown).

Table 8.8 Preventive medications reported by Gulf War veterans

Preventive medications (N=1418)	n	(%)
Anti-nerve agent pills (NAPS)		
No	371	(26.2)
Don't know	318	(22.4)
Yes	728	(51.4)
1-80 pills taken	152	(33.3)*
81-180 pills taken	156	(34.2)*
> 180 pills taken	148	(32.5)*
Anti-biological warfare tablets		
No	540	(38.2)
Don't know	793	(56.1)
Yes	81	(5.7)
1-21 days	15	(25.4)†
22-80 days	24	(40.7)†
>80 days	20	(33.9)†
Antimalarials		
No	283	(20.0)
Don't know	544	(38.2)
Yes	586	(41.5)

* Percentage of the 456 subjects who provided this information
† Percentage of the 59 subjects who provided this information

8.3.4 Self-reported psychological stressors during Gulf War service and during non-Gulf War service

Psychological stressors experienced by Gulf War veterans during the Gulf War deployment, and by all study participants during military service activities in general were assessed with the Military Service Experience (MSE) section of the postal questionnaire. The MSE questionnaire comprised 44 items, each representing a potentially stressful activity or experience, possibly relevant to ADF military service experience. The questions covered such themes as actual or threatened physical threat, exposure to, or responsibility for the death or suffering of others, feelings of helplessness and lack of control, poor preparation, malevolent environment, lack of support and lack of unit cohesion.

A complete description of the development and design of the MSE questionnaire is provided at section 5.6.1.2.4 chapter 5.

The frequency of positive ('Yes') responses to individual items on the MSE questionnaire are shown in Table 8.9 for Gulf War veterans in relation to Gulf War service, and for Gulf War

veterans and comparison group subjects in relation to military service outside of the Gulf War (non-Gulf War service). The 44 items are shown in decreasing order of frequency for Gulf War veterans in relation to Gulf War service; ie the most frequently reported Gulf War experiences are shown at the top of Table 8.9. A graphical presentation of the data in Table 8.9 is shown in Figure 8.1.

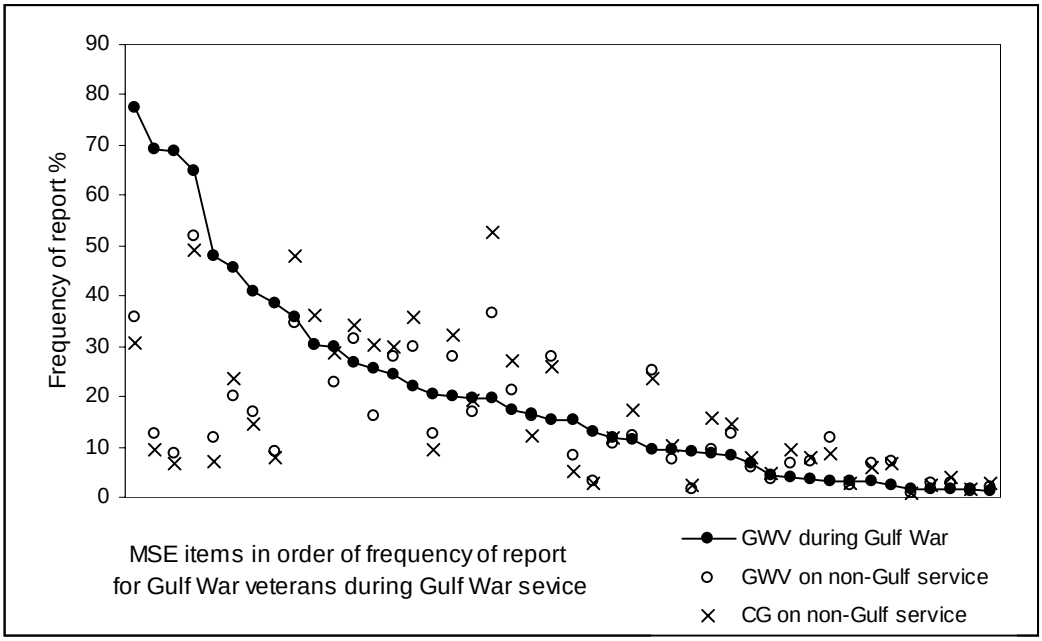
Table 8.9 Military Service Experience questionnaire items reported by Gulf War veterans in relation to the Gulf War deployment, and by Gulf War veterans and the comparison group in relation to non-Gulf War military service

Military Service Experience questionnaire						
	Gulf War service		Non-Gulf War service			
	Gulf War veterans (N=1424)		Gulf War veterans (N=1424)		Comparison group (N=1548)	
MSE item	**N**	**(%)***	**n**	**(%)***	**n**	**(%)***
You were on a ship or aircraft (including a helicopter) passing through hostile waters or air space.	1083	(77.5)	482	(35.6)	476	(30.8)
You were in fear of artillery, missile, SCUD rocket or bomb attack.	974	(69.2)	169	(12.4)	145	(9.4)
You were on formal alert for, or felt in threat of nuclear, biological or chemical agent attack.	965	(68.8)	118	(8.6)	104	(6.7)
You felt cut off or separated from family or significant others.	915	(64.8)	713	(51.9)	759	(49.1)
On board a ship you feared death, injury or entrapment below the waterline as a result of missile attack or hitting a sea-mine.	679	(48.0)	164	(11.9)	109	(7.1)
You were in fear for your life.	641	(45.4)	274	(20.0)	363	(23.5)
You were responsible for detecting incoming attacks or for spotting land or sea-mines, where a mistake could place the lives of others at risk.	578	(40.9)	232	(16.9)	223	(14.4)
You encountered undetonated mines, including sea mines, or booby traps while on patrol or at your duty station.	541	(38.4)	125	(9.1)	120	(7.8)
You experienced a ‘near miss’ or ‘very close call’ incident where you were in imminent danger of being injured or killed.	504	(35.9)	472	(34.5)	734	(47.8)
Your supplies or equipment were inadequate, insufficient or faulty.	429	(30.4)	418	(30.3)	555	(36.0)
Artillery, rockets, missiles, mines or something similar, exploded in the air, in the water or on the ground close to you.	418	(29.9)	313	(22.9)	440	(28.5)
You have suffered ill-effects of extreme heat or extreme cold.	380	(26.9)	430	(31.5)	529	(34.3)
You had difficulty breathing as a result of exposure to oil, smoke, fumes, dust or other contaminants in the air.	360	(25.6)	223	(16.2)	465	(30.2)
You were required to detonate, deactivate or otherwise handle live missiles, mines, bombs or other explosive devices.	344	(24.4)	385	(28.0)	459	(29.8)
You experienced lack of leadership in your team, crew or unit.	313	(22.2)	410	(29.8)	552	(35.8)
You felt overwhelmed by the level of destruction or devastation or disease around you.	286	(20.3)	174	(12.7)	143	(9.3)
You felt lack of togetherness or cohesion in your team or unit.	281	(19.9)	383	(27.8)	495	(32.1)
You felt not sufficiently trained or prepared for military activities.	280	(19.8)	231	(16.8)	298	(19.3)
You sustained an injury that required medical treatment.	276	(19.7)	498	(36.4)	806	(52.5)

Military Service Experience questionnaire						
	Gulf War service		Non-Gulf War service			
	Gulf War veterans (N=1424)		Gulf War veterans (N=1424)		Comparison group (N=1548)	
MSE item	**N**	**(%)***	**n**	**(%)***	**n**	**(%)***
You had to work, dive or bathe in water contaminated with smoke, oil, sewerage or other chemical or biological agents.	239	(17.1)	292	(21.2)	417	(27.0)
You feared attack from bandits, rebels or other local militia groups.	235	(16.7)	222	(16.1)	189	(12.2)
You saw Defence personnel or civilians who were killed, dead, dying or maimed.	217	(15.5)	382	(27.8)	398	(25.8)
You felt an overwhelming inability to protect yourself or others from harm.	216	(15.2)	113	(8.2)	81	(5.2)
You carried out your duties wearing NBC suits (not including training exercises).	184	(13.0)	43	(3.1)	44	(2.8)
You had to board hostile vessels at sea.	166	(11.8)	147	(10.7)	181	(11.7)
You suffered burns or rashes on your skin as a result of exposure to oil or other chemicals in the air.	161	(11.5)	164	(12.0)	266	(17.2)
You were on a ship which suffered a collision or was otherwise damaged or sunk during deployment.	131	(9.4)	344	(25.0)	364	(23.7)
You felt alienated from other military personnel around you.	131	(9.3)	103	(7.5)	159	(10.3)
You were exposed to nuclear, biological or chemical warfare.	121	(9.0)	22	(1.6)	39	(2.5)
You had to eat food or drink water contaminated with smoke, oil, sewerage or other chemical or biological agents.	121	(8.6)	131	(9.6)	243	(15.7)
You handled or came into contact with POWs or displaced refugees.	118	(8.4)	173	(12.5)	223	(14.4)
You came under small arms fire.	93	(6.6)	80	(5.8)	122	(7.9)
Operational rules of engagement prevented you from taking action which could protect you or others from harm.	63	(4.5)	49	(3.6)	76	(4.9)
You were required to live in squalid, unsanitary or disease-ridden conditions.	55	(3.9)	92	(6.7)	145	(9.4)
You were attacked by civilians, bandits or other local militia groups.	51	(3.6)	96	(7.0)	124	(8.0)
You handled, buried or exhumed human bodies.	43	(3.1)	162	(11.8)	131	(8.5)
You were required to administer medical aid for which you were not adequately trained or equipped, eg geriatrics, paediatrics, palliative care.	44	(3.1)	35	(2.5)	41	(2.7)
You witnessed violent attacks on civilians including rape or other assaults.	43	(3.1)	92	(6.7)	92	(6.0)
You sat with or cared for someone who was dying.	32	(2.3)	97	(7.1)	100	(6.5)
You were deployed to a combat situation against your will.	23	(1.6)	12	(0.9)	14	(0.9)
You had to decide who would receive life-saving medical care.	23	(1.6)	40	(2.9)	39	(2.5)
You made a leadership decision which you think resulted in the death or injury of someone.	20	(1.4)	37	(2.7)	59	(3.8)
You killed someone or think you might have killed someone.	19	(1.4)	16	(1.2)	22	(1.4)
You were sexually harassed.	15	(1.1)	28	(2.0)	45	(2.9)

*The value of N from which each percentage is derived, varies by up to 5% fewer respondents depending on the numbers of participants who answered each item.

Figure 8.1 Frequency of MSE questionnaire items reported by Gulf War veterans in relation to the Gulf War deployment, and by Gulf War veterans (GWV) and the comparison group (CG) in relation to non-Gulf War military service



8.3.4.1 Psychological stressors during Gulf War service

The MSE item reported most frequently for Gulf War service was being on board a ship or aircraft passing through hostile waters or airspace (Table 8.9). Four out of the next five MSE items reported most frequently for Gulf War service involved personal fear or threat; they were fear of artillery attack, threat of chemical or biological attack, fear of death or injury below the waterline on a ship, and fear for one's life. Other frequently reported items included feelings of separation from family and significant others, responsibility for detecting incoming attack, close encounters with undetonated mines, other exploding rockets or mines, a near miss incident with imminent danger of death or injury and inadequate or faulty equipment.

Some military service experiences were much more likely to be reported in relation to Gulf War service than in relation to any non-Gulf War service. Figure 8.1 shows that seven out of the eight MSE items most frequently reported by Gulf War veterans during Gulf War service, were quite unique to this ADF deployment and infrequently reported by either group in relation to non-Gulf war service. Gulf War veterans, during Gulf War service, were eight times more likely to report being on formal alert for or under threat from nuclear, chemical or biological agent attack, than Gulf War veterans or comparison group subjects in relation to non-Gulf War service. MSE items reported more than four times more commonly during Gulf War service include experiences in relation to exposure to nuclear, chemical or biological warfare, being in fear of artillery, missile, SCUD or bomb attack, encountering undetonated mines, sea-mines or booby traps, carrying out duties wearing full protective clothing (NBC suits) and fearing death, injury or entrapment below the waterline on a ship. Common MSE items reported more than twice as often during Gulf War service were experiences in relation to responsibility for detecting incoming attacks or for spotting mines where a mistake could place the lives of others at risk, fear for one's life and being on a ship or aircraft passing through hostile waters or airspace.

In contrast, many of the remaining MSE items were much less likely to be reported during Gulf War service, when compared with those reported during non-Gulf service by both the Gulf War veterans and the comparison group. Items reported less than half as often include ship collisions or damage, leadership decisions resulting in death or injury, handling of human bodies, attack by civilians, bandits or local militia, sexual harassment, witnessing of violent attacks on civilians, sitting with or caring for someone dying, living in squalid, unsanitary or disease ridden conditions and sustainment of an injury requiring medical treatment.

The MSE questionnaire was scored by summing the number of 'Yes' responses for each person. Subjects received a score ranging from 0 to 44. Table 8.10 shows that Gulf War veterans, in relation to the Gulf War, answered 'Yes' to more MSE items than they or the comparison group did in relation to non-Gulf War service.

Table 8.10 Military Service Experience questionnaire scores

Military Service Experience questionnaire						
	Gulf War service		**Non-Gulf War service**			
	Gulf War veterans (N=1420)		**Gulf War veterans (N=1389)**		**Comparison group (N=1547)**	
	Median	**Range**	**Median**	**Range**	**Median**	**Range**
Median MSE item score	8	0-33	5	0-33	6	0-35
Categories of MSE item score	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
0 - 4	320	(23)	600	(43)	585	(38)
5 – 8	415	(29)	352	(25)	414	(27)
9 – 12	316	(22)	242	(17)	273	(18)
>12	369	(26)	195	(14)	275	(18)

For Gulf War service, median MSE questionnaire scores are shown for Gulf War veterans across age categories, service type and rank categories in Table 8.11. MSE questionnaire items were reported most frequently by the younger age groups, by the Army and by the lowest ranked group.

Table 8.11 Median and range MSE questionnaire scores for Gulf War veterans by age, service type and rank

Gulf War service MSE questionnaire score		
	Gulf War veterans	
	Median	(Range)
Age		
< 20	10	(0-25)
20-24	8	(0-28)
25-34	8	(0-33)
≥ 35	7	(0-30)
Service Type		
Navy	8	(0-33)
Army	11	(1-30)
Air Force	4	(0-29)
Rank		
Officer	8	(0-27)
Other rank-supervisory	8	(0-30)
Other rank-non supervisory	9	(0-33)

8.3.4.2 Psychological stressors during non-Gulf War service

In relation to military service outside of the Gulf War (non-Gulf War service), Gulf War veterans and comparison group subjects had similar rates of many of the experiences itemised in the MSE questionnaire (see Table 8.9 and Figure 8.1). Some non-Gulf War service experiences, however, were reported noticeably more often by comparison group subjects, in relation to lack of leadership, faulty or inadequate equipment, a 'near miss' with imminent danger of being injured or killed, and an injury requiring medical treatment. Gulf War veterans were somewhat more likely to report being on a ship or aircraft passing through hostile waters or airspace, during non-Gulf War service, relative to the comparison group.

8.3.5 Self reported chemical and environmental exposures during the Gulf War and other active deployments

In relation to the Gulf War deployment and other active deployments, study participants responded to a 28 item chemical and environmental exposure questionnaire. A broad range of exposures were covered, including depleted uranium, CARC paint, contaminated food or water, dust storms, intense smoke, fuels, solvents, sunscreens, exhaust emissions, insects, pesticides, insect repellents and chemical warfare agents. Questions about the use of respirators and wearing of NBC suits were also included.

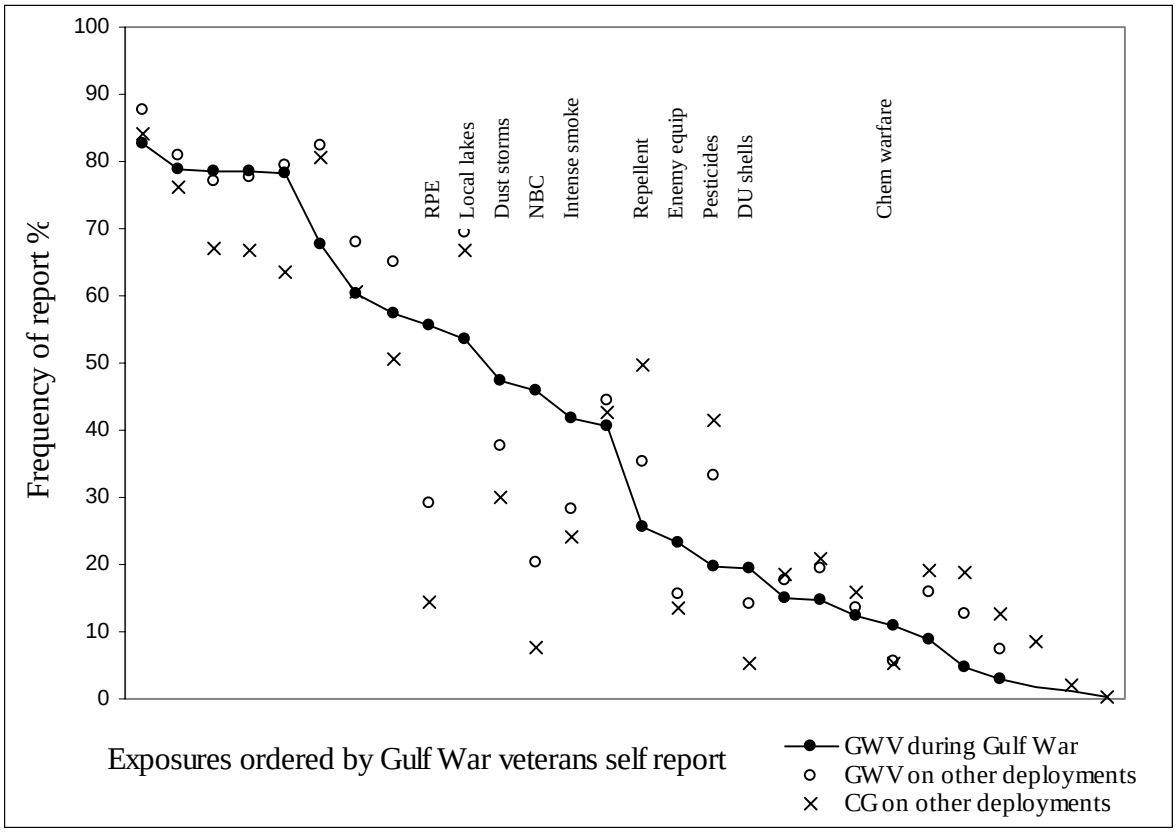
The results are shown in Table 8.12 and Figure 8.2. The table and figure are ordered in decreasing frequency for items reported by Gulf War veterans in relation to their Gulf War deployment.

Table 8.12 Chemical and environmental exposure questionnaire items reported by Gulf War veterans in relation to the Gulf War deployment, and by Gulf War veterans and the comparison group in relation to non-Gulf War active deployments

	Gulf War deployment		Non-Gulf War deployments			
	Gulf War veterans (N=1424)*		Gulf War veterans (N=625)*		Comparison group (N=514)*	
Exposures	**n**	**(%)***	**n**	**(%)***	**n**	**(%)***
Sunscreen when outdoors	1170	(82.7)	534	(87.7)	429	(84.0)
Solvents, oils, diesel or other fuel on the skin	1116	(78.9)	494	(81.0)	390	(76.3)
Exposed to solvents	1111	(78.6)	469	(77.0)	343	(67.1)
Refuelling	1107	(78.4)	473	(77.7)	342	(66.9)
Ate locally sourced, non-military issue food	1101	(78.2)	485	(79.5)	323	(63.5)
Bitten by flies, sand flies, fleas, mosquitoes etc	956	(67.7)	502	(82.4)	412	(80.6)
Engine exhaust irritated the eyes	847	(60.2)	415	(68.0)	309	(60.7)
Locally sourced, military issue food	803	(57.4)	397	(65.0)	256	(50.5)
Use of respiratory protective equipment (RPE)	783	(55.7)	174	(29.1)	72	(14.3)
Swum or bathed in local lakes, rivers or the sea	752	(53.4)	424	(69.4)	341	(66.7)
Exposed to dust storms	666	(47.5)	228	(37.6)	152	(30.0)
Used a chemical protective suit (NBC suit)	646	(45.9)	121	(20.4)	39	(7.7)
Exposed to intense smoke	585	(41.8)	172	(28.3)	122	(24.1)
Drank water from local taps or wells	569	(40.5)	271	(44.4)	218	(42.7)
Used a personal insect repellent	363	(25.7)	221	(36.1)	253	(49.8)
Entered, or inspected, captured or destroyed enemy equipment including tanks	320	(23.2)	95	(15.7)	69	(13.5)
Lived/worked in an area where pesticide sprayed/fogged	276	(19.6)	201	(33.1)	212	(41.5)
Contact with depleted uranium shell casings	269	(19.3)	86	(14.2)	27	(5.3)
Showered in water with fuel in it	209	(14.9)	108	(17.7)	94	(18.4)
Drank water with oil in it	174	(12.4)	83	(13.6)	81	(15.9)
Applied pesticides	161	(11.4)	110	(17.8)	107	(20.9)
In an area where chemical warfare agents had probably been used	152	(10.8)	34	(5.6)	27	(5.3)
Stung or bitten by spiders, scorpions or other bugs	122	(8.7)	97	(15.9)	98	(19.2)
Clothing or uniforms treated with pesticides	68	(4.8)	76	(12.6)	96	(18.8)
Tent treated with pesticides	41	(2.9)	45	(7.5)	64	(12.6)
Sleeping bag treated with pesticides	24	(1.7)	26	(4.3)	43	(8.4)
Contact with wet CARC paint	18	(1.3)	6	(1.0)	11	(2.2)
Wore a flea collar	6	(0.4)	1	(0.2)	1	(0.2)

* The value of N from which each percentage is derived, varies depending on the numbers of participants who answered each item

Figure 8.2 Frequency of chemical and environmental exposure questionnaire items reported by Gulf War veterans (GWV) in relation to the Gulf War deployment, and by Gulf War veterans and the comparison group (CG) in relation to non-Gulf War active deployments



8.3.5.1 Self-reported chemical and environmental exposures during the Gulf War

Many items, representing several different types of exposures, were reported by large proportions of Gulf War veterans in relation to the Gulf War deployment (Figure 8.2). More than 70% of Gulf War veterans, for example, reported exposure to sunscreens, solvents, fuels and locally sourced foods. More than 60% of veterans reported exposure to insects and engine exhausts.

Some specific items were notably more common in the Gulf War deployment than in non-Gulf War active deployments. Figure 8.2 identifies exposures that veterans reported experiencing more or less frequently during the Gulf War deployment compared to other deployments. Exposure to dust storms, intense smoke, entering or inspecting destroyed enemy equipment and contact with depleted uranium shell casings were more commonly reported as experiences during the Gulf War deployment than during other deployments.

Being in an area where chemical warfare agents had probably been used, and the related use of personal protective equipment, were reported by less than 11% of Gulf War veterans but were reported twice as commonly during the Gulf War deployment as during non-Gulf War active deployments. Being in an area where chemical warfare agents had probably been used was, however, reported by half of Operation Habitat personnel. Only 1.5% of veterans reported being near Khamisiyah when it was demolished, which could have involved

exposure to low levels of chemical warfare agents. The most common reason identified by 43% of the veterans for believing that they had been in an area where chemical warfare agents had been used, was because the veterans had been "told so". Only three veterans reported feeling ill at the time. Reasons for use of respiratory protective equipment (RPE) and chemical protective clothing were most commonly reported as "for training" (39% and 52% respectively) or because "alarms went off" (35% and 32% respectively).

Using responses to the items on the chemical and environmental questionnaire (Table 8.12), Gulf War veterans were given a chemical and environmental exposure score (C&E score). This was calculated for each veteran by summing the 'yes' responses to the 28 items. Subjects received a C&E score of between 0 and 28. The mean C&E scores are shown in Table 8.13 for the total Gulf War veteran population, for subgroups of service type, rank and age and for veterans whose deployment ended before or after the commencement of the air war on 17th January 1991.

Gulf War veterans reported exposure to an average of 10.2 chemical and environmental exposure questionnaire items. Mean C&E score were highest for Army veterans and lowest for Air Force veterans. However, mean C&E score varied little across subgroups of rank and age and did not differ according to whether subjects completed their deployment before or after commencement of the air war.

Table 8.13 Mean C&E score for Gulf War veterans in relation to the Gulf War deployment.

	C&E score	
	Mean	**(SD)**
Total Gulf War veterans	10.2	(4.2)
Service type		
Navy	10.4	(3.9)
Army	12.0	(5.0)
Air Force	6.5	(4.6)
Rank		
Officers	9.4	(4.5)
Other ranks-supervisory	10.4	(4.3)
Other ranks-non supervisory	10.5	(3.8)
Age		
<20 years	10.5	(3.7)
20 - <25 years	10.5	(3.8)
25 - <35 years	10.2	(4.3)
≥ 35 years	9.5	(4.9)
Deployment era		
Deployment complete before 17th Jan 1991	9.6	(3.9)
Deployment completed after 17th Jan 1991	10.5	(4.3)

8.3.5.2 Self-reported chemical and environmental exposures on other active deployments

Many exposures most commonly reported in relation to the Gulf War deployment, were also most commonly reported in relation to non-Gulf War active deployments by both study groups (Figure 8.2). When on non-Gulf War active deployments, Gulf War veterans more often reported slightly higher levels of exposures than the comparison group, although the frequencies of report were similar for most items. Gulf War veterans, in relation to non-Gulf War active deployments, reported more refuelling, eating locally sourced food, engine exhaust which irritated the eyes, use of personal protective equipment including NBC suits, contact with depleted uranium shell casings and exposure to dust storms. In non-Gulf War active deployments, Gulf War veterans were less likely than the comparison group to report exposure to personal insect repellents, living or working in pesticide sprayed or fogged areas, and having their clothing, sleeping bags or beds treated with pesticides.

Several exposures which were reported infrequently by Gulf War veterans in relation to the Gulf War deployment, were also reported infrequently in relation to non-Gulf War active deployments by both study groups (Figure 8.2).

8.3.6 Development of chemical and environmental exposure metrics related to the Gulf War deployment

Several exposure metrics were constructed from responses to the chemical and environmental exposures questionnaire, and from other questions in the postal questionnaire for use in subsequent health outcome results chapters of this report. These are yes/no exposure metrics and are shown in Table 8.14. Some metrics identify small groups of veterans, for example few veterans were exposed to pesticides during the Gulf War, whilst self-reported exposures to solvents was very common.

Table 8.14 Exposure metrics for Gulf War veterans during the Gulf War

Exposure metric	Yes	(%)
Solvent exposure	1111	(78.6)
SMOIL any	754	(53.9)
SMOIL Low	627	(44.8)
SMOIL High	127	(9.1)
Dust storms	666	(47.5)
Pesticides	380	(27.0)
Insect repellent	363	(25.7)
Possible DU exposure	218	(15.5)
In area where chemical warfare agent used	152	(10.8)

There was a single question in the questionnaire about exposure to each of the following exposures; solvents, smoke from oil well fires (SMOIL), dust storms, insect repellent and being in an area where chemical warfare agents had been used. Gulf War veterans were considered to have self-reported a particular exposure if they answered yes to that question. More than half of the Gulf War veterans reported exposure to SMOIL. These veterans can be divided into a large group who had ‘low’ exposure and a smaller group, who were classified as having had ‘high’ exposure because they reported exposure to SMOIL for more than five hours per day on ten or more days in total.

Other metrics were more complex. There were seven questions about pesticide use, and Gulf War veterans were considered to be exposed if they answered yes to any one question.

A small number of Gulf War veterans were considered to have self-reported possible depleted uranium (DU) exposure because they reported being at Camp Doha when the tank compound caught fire and were involved in the subsequent clean up operations, **or** they reported being in Kuwait, or in the areas of the battle zones after 17th January 1991 **and** they reported contact with destroyed enemy equipment or contact with DU shells. 10.8% of veterans reported having been in an area where chemical warfare agents had probably been used.

If a veteran did not know whether he had experienced a specific exposure, for the purpose of this metric, he was grouped with those who reported no exposure. For most of the exposures, veterans could be expected to recall significant exposure for example to SMOIL or to fuels. If they had been unaware of exposure to these agents, the exposure would probably have been low. There was, however, a higher proportion of veterans stating 'don't know' for chemical warfare exposure than for most other exposures.

The Gulf War veterans were divided into those whose deployment was completed before 17th January, the date when the air war started, and those whose Gulf War service was not completed by this date. The proportion of each of these groups categorised as exposed using our exposure metrics are presented in Table 8.15. SMOIL exposure was reported by 63.7% of the group whose deployment was not complete by 17th January but 22.1% of veterans whose deployment was completed by this date also reported this exposure.

As expected, veterans whose deployment was not completed by 17th January were more likely to report exposure to DU and/or having been in an area where chemical weapons had been used. A similar proportion of both groups of veterans reported exposure to solvents and insect repellents. Differences in rates of pesticide use may be accounted for by differences in the groups who were deployed within the two time frames, for example Operation Habitat took place in May and June 1991. 84.9% of Operation Habitat personnel used or were exposed to pesticides compared to 25.2% of other veterans.

Table 8.15 Exposure metrics for Gulf War veterans during the Gulf War by period of service

Exposure metric	**Deployment completed before January 17th 1991 (N=331)**		**Deployment not completed before January 17th 1991 (N=1092)**	
	Yes	**(%)**	**Yes**	**(%)**
Solvent exposure	257	(78.1)	853	(78.7)
SMOIL any	72	(22.1)	682	(63.7)
Dust storms	132	(40.2)	533	(49.7)
Pesticides	65	(20.2)	313	(29.0)
Insect repellent	80	(24.2)	282	(26.1)
Possible DU exposure	26	(7.9)	192	(17.9)
In area where chemical warfare agent used	11	(3.4)	141	(13.1)

8.3.7 Other occupational exposures during the whole military career and during civilian careers

Participants were asked to state whether they had ever been members of the Country Fire Authority. 81 (6.1%) of Gulf War veterans and 87 (6%) of the comparison group reported that they had been members of the Country Fire Authority.

For all military postings of three months or more, participants reported whether they regularly worked with or handled pesticides, solvents, fuels or engine exhaust. The results are shown in Table 8.16.

For all civilian jobs held for six months or more, participants reported whether they worked with, handled or were otherwise exposed to pesticides, solvents, fuels, engine exhaust, infectious diseases or trauma to others (such as violence, grief or death of others). These results are shown in Table 8.17.

Table 8.16 Self reported exposures during military postings of 3 months or more.

Military occupational exposures				
	Gulf War veterans		**Comparison group**	
	n	**(%)**	**n**	**(%)**
Pesticides	274	(19.2)	246	(15.9)
Fuels	884	(62.1)	937	(60.5)
Engine Exhaust	852	(59.8)	919	(59.4)
Solvents	1053	(73.9)	1048	(67.7)

Table 8.17 Self reported exposures during civilian jobs held for 6 months or more.

Civilian occupational exposures				
	Gulf War veterans		**Comparison group**	
	n	**(%)**	**n**	**(%)**
Pesticides	123	(8.9)	148	(9.8)
Fuels	370	(26.6)	459	(30.2)
Engine Exhaust	354	(25.5)	459	(30.1)
Solvents	417	(30.0)	508	(33.4)
Infectious diseases	137	(9.9)	119	(7.9)
Trauma	153	(11.0)	138	(9.2)

Very similar proportions of the two study groups reported exposure for each of the items. Exposures to fuels, solvents and engine exhausts were fairly high in both study groups for both their military postings and any civilian occupations. For military exposures, prevalence was consistently higher for the Gulf War veterans, but there was no consistent direction in relation to civilian exposures.

8.4 Discussion

Male Gulf War veterans report experiencing a range of chemical and environmental exposures, psychological stressors, immunisations and preventive medications in relation to

the Gulf War deployment. Some of these exposures, such as to SMOIL and taking NAPS tablets are exclusive to the Gulf War deployment and highlight its unique nature. Several other exposures were experienced much more frequently during the Gulf War deployment compared to other deployments for example the use of RPE or NBC suits which are significant stressors in themselves. A number of psychological stressors such as fearing death or injury, fear of attack and of exposure to nuclear, chemical or biological warfare were much more common experiences during the Gulf War compared to the remainder of the veterans' military careers. There were a number of chemical and environmental exposures that were frequently experienced both during the Gulf War and also frequently during other deployments. These include exposure to fuel, solvents and sunscreen.

Psychological stressors during the Gulf War were most commonly associated with fear of death or injury, threat of attack or being in a hostile environment. These were notably more common during the Gulf War deployment than during other non-Gulf War military service. Threat in relation to nuclear, biological or chemical attack or artillery or SCUD or other bomb attack, encountering of undetonated mines including sea mines and fear of entrapment below the waterline on a ship were particularly unique to the Gulf War environment and rarely reported during non-Gulf War service. Actual incidents such as killing someone, coming under direct attack, witnessing dead or maimed persons or violent attacks and handling human remains, whilst likely to be extremely stressful events for those who experienced them, were relatively rare during the Gulf War deployment for Australian veterans. These items have been reported much more commonly by overseas Gulf War ground forces.[20, 21]

The lack of actual incidents should not minimise the significance of stressors described more commonly by Australian Gulf War veterans. When considering mental disability claims the Repatriation Medical Authority (RMA) define 'severe stressors' as including threat of serious injury or death, threat to another person's physical integrity and engagement with the enemy. The RMA criteria for posttraumatic stress disorder, for example, derived from DSM-IV,[308] includes exposure to a traumatic event in which the person experienced, witnessed or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the integrity of self or others. The response must involve fear, helplessness or horror. Stressors involving fear and threat are common in the Australian Gulf War deployment based on self-reported responses to the MSE questionnaire. Other common stressors reported by Australian Gulf War veterans, including being overwhelmed by the level of destruction, devastation or disease and an inability to protect oneself or others from harm, may well be consistent with a response involving helplessness or horror.

The fact that some psychological stressors were relatively rare during non-Gulf War service should be considered in the light of evidence that only 44% of Gulf War veterans and one third of the comparison group had been on a warlike active deployment other than the Gulf War. Active deployments are the most likely period of a military career to result in these kinds of stressful experiences.

Ten percent of Australian veterans reported having been immunised against smallpox during the Gulf War period. This is very unlikely as it was not in use as an immunisation during the Gulf War period, although individuals may have been immunised at some time in the past. Neither smallpox, nor plague, nor anthrax immunisations were listed as recommended immunisations on the message telex sent by the Surgeon General ADF, see chapter 8. Almost 50% of Australian veterans believed that they had been immunised against plague compared to 26% of UK veterans.[21] 15% of Australian veterans reported immunisation against anthrax (another 58% were unsure) compared to 57% of UK veterans.[21] The percentage is much higher for veterans who deployed in Damask II than on other

deployments. Those veterans who were deployed with US and UK forces may have received immunisations with the forces from those countries.

Australian Gulf War veterans were more likely to report having been immunised in preparation for the Gulf War compared to UK Gulf War veterans. Only 8% report receiving no immunisations but 40% of UK veterans reported receiving no immunisations.[21] A similar proportion of Australian and UK veterans received more than 6 immunisations, 27% of Australians compared to 30% of UK veterans (but only 19% of the UK Navy veterans).[28] Australian Gulf War veterans were more likely than UK veterans to have retained their record of immunisation. 32% of UK veterans had their immunisation records[21] compared to 51% of Australian veterans.

Fifty one percent of Australian veterans recalled taking NAPS. This is at the low end of the range reported in UK and US veterans of whom between 52% and 82% recalled taking PB.[16, 19, 21, 28, 33, 35, 38]

Australian Gulf War veterans reported exposure to several chemical and environmental exposures at similar rates to veterans from other countries. It might be expected that a mainly naval contingent would have had less exposure to some types of agents, eg dust storms or insect repellent, than would personnel on land. The data presented here refer to whether or not there was *any* exposure, however, rather than the extent of exposure.

The proportion of Australian veterans reporting exposure to SMOIL, pesticides, petroleum products or eating contaminated or local food were, in each case, within the ranges reported for Danish, UK or US veterans.[16, 19-21, 28, 32, 33, 35, 36, 38, 41, 46]

The majority of Australian Gulf War veterans, like US and UK veterans, recalled wearing chemical protective clothing or had heard chemical alarms.[20, 21] If the electronic alarm activated, ADF personnel in the vicinity should have used chemical protective clothing including RPE. Australian ships' logs recorded chemical alarm activation, some were exercises and the remainder were found to be false alarms.[2] About 10% of veterans considered that they may have been exposed to chemical warfare agents. This is within the range reported by US veterans.[16, 20, 33, 35, 38, 351]

Higher exposures to local water, paint, solvents and skin exposure to solvents, diesel or petrochemicals were reported by Australian veterans compared to studies of overseas veterans.[20, 21, 33] This may be because many of the Navy veterans were involved in refueling from supply ships or working in ship's engine rooms. A high proportion (40%), reported drinking water from local taps or wells compared with 2 to 31% of US personnel,[20] but this is similar to rates in other ADF deployments.

Exposure to repellents was reported by 25.6% of Australian veterans. This value is at the low end of the range reported for other countries' veterans.[19-21, 28, 38, 94]

CARC paint was only used by one unit of US soldiers and some civilians in the USA but up to half of US veterans reported exposure to CARC.[20, 33, 46] It is unlikely that any members of the ADF were involved, although 1.3% reported contact. Veterans may recall painting or spraying vehicles and believed or suspected that this was CARC paint.

The exposure metrics developed for use in the health outcomes results chapters that follow, rely on self-reported exposure during the Gulf War. They do not take into account exposures that an individual may have had outside the Gulf. Many of these metrics are based on a single question and thus do not differentiate individuals by extent or frequency of exposure. This may result in some misclassification of individuals, grouping those with very low

exposure with others who were more highly exposed. This is important because such non-differential misclassification tends to reduce any observed odds ratios.[352]

Reporting of chemical and environmental exposures was not related to age or rank but there was some relationship with service types; with Air Force veterans less likely to report exposures. Psychological stressors were reported most frequently by the younger age groups and by the Army.

Male Gulf War veterans were more likely than the comparison group to have experienced one or more active deployments other than the Gulf War. However, adding the number of deployments as we have done in our study, assumes that all deployments are similar; but it is probable that some deployments were more stressful or involved more exposures than others.

Gulf War veterans and comparison group subjects who went on other deployments are similar in relation to their chemical and environmental exposures reported from these deployments. Gulf War veterans and comparison group subjects are similar in the occupational exposures reported in association with the rest of their military and civilian histories. The two groups are similar in respect of the psychological stressors experienced outside of the Gulf War.

Self-reported exposure and experiences recalled over ten years may be unreliable. Reliability of the recall of self-reported occupational exposures improves if people are prompted with a list of exposures which we did in our study.[252] In relation to exposure reporting during the Gulf War there are no gold standards against which reports can be prepared. There is almost no available documentation of what exposures veterans experienced during their Gulf War service. However we can make some assessment of the reliability of the reported exposures by comparing the rates of reports among veterans whose deployments were or were not completed by 17th January. Over 20% of veterans whose deployment was completed by 17th January reported exposure to SMOIL. This exposure is unlikely considering that the oil wells were set on fire by the retreating Iraqis, starting probably in late January.[81] The rates of report for solvent exposure or insect repellent use are similar for those veterans whose deployments were and were not complete by 17th January (Table 8.15). We would not have expected these to differ. Few veterans whose deployments were completed before 17th January report possible DU exposure, this is consistent with the fact that the open hostilities had not commenced. Some differences in exposure reporting rates between the two groups could be accounted for by differences in weather, for example dust storms, others could be attributable to different duties carried out by the ADF before and after the ground war. Operation Habitat personnel are in the latter group and they are more likely to report being in an area where chemical weapons had been used and are more likely to have used pesticides.

If over-reporting was a major problem amongst Gulf War veterans, we would expect to find some increase in reporting of exposures over the whole range of exposures. This is generally not evident in relation to reports of exposures during non-Gulf War service. However, a number of veterans reported having plague, anthrax and smallpox immunisations. They were not listed on the ADF telex and it is unlikely that smallpox immunisation was available at this time. The similarly low rate of anthrax immunisations reported by those deployed on USNS *Comfort*, Damask I and Damask III and the higher rate reported by those deployed on Damask II suggest that the immunisation was more likely to have been used on Damask II. The similarity in recall of most chemical and environmental exposures between the Gulf War veterans' and comparison group in their on deployments other than the Gulf War and the Gulf War veterans' during the Gulf War suggests that over-reporting of these exposures is not a major factor. Gulf War veterans responded 'Yes' to slightly fewer stressors, in relation to

non-Gulf War service, than the comparison group. This again is suggestive that Gulf War veterans as a whole do not over-report most exposures.

Many veterans will have been co-exposed to several chemical and environmental exposures, to immunisations and medications and to psychological stressors. For example some veterans reported that they used RPE and protective clothing when exposed to SMOIL, dust storms or after hearing chemical alarms. The identification of which of these co-existing exposures or experiences is associated with any specific health outcome could therefore be problematic.

In choosing which exposure metrics to apply in subsequent health outcome chapters we have applied the following general principles.

- Subanalyses by exposure within the Gulf War group were normally only carried out where there was a difference in health outcome between the Gulf War veterans and the comparison group.
- There needed to be sufficient prevalence of exposure in the Gulf War group to warrant any subanalyses.
- There needed to be a plausible biological link between the health outcome and the exposure being investigated.
- Subanalyses were also carried out where there was an *a priori* reason to do so, for example if other studies of Gulf War veterans had found an association between a health outcome and an exposure or experience.

8.4.1 Summary of findings

In summary and relation to the specific research questions for this chapter:

Male Gulf War veterans report experiencing a range of chemical and environmental exposures, psychological stressors, immunisations and preventive medications in relation to the Gulf War. Among the most frequently reported exposures are:

- typhoid and cholera immunisations,
- taking NAPS tablets,
- psychological stressors, such as being in hostile waters or air space, being in fear of artillery, missile, SCUD or bomb attack, experiencing the threat of nuclear, biological or chemical agent attack, being on a ship and in fear of death, injury or entrapment below the waterline,
- sunscreen, solvents, fuel, SMOIL, dust storms, and the use of RPE and NBC protective equipment.

The exposures that were first encountered by ADF personnel in relation to the Gulf War or were unique to the Gulf War are NAPS tablets, exposure to SMOIL, DU, threat of nuclear, biological or chemical agent attack and consequent use of NBC suits and RPE.

C&E exposure scores are not related to age or rank but there is some relationship with service type. Psychological stressors were reported most frequently by the younger age groups and by the Army.

Male Gulf War veterans were more likely than the comparison group to have experienced one or more active deployments other than the Gulf War.

Gulf War veterans and comparison group subjects who went on other deployments are similar in relation to their chemical and environmental exposures reported from these

deployments and in the occupational exposures reported in association with the rest of their military and civilian histories. The two groups are similar in respect of the psychological stressors experienced outside of the Gulf War.